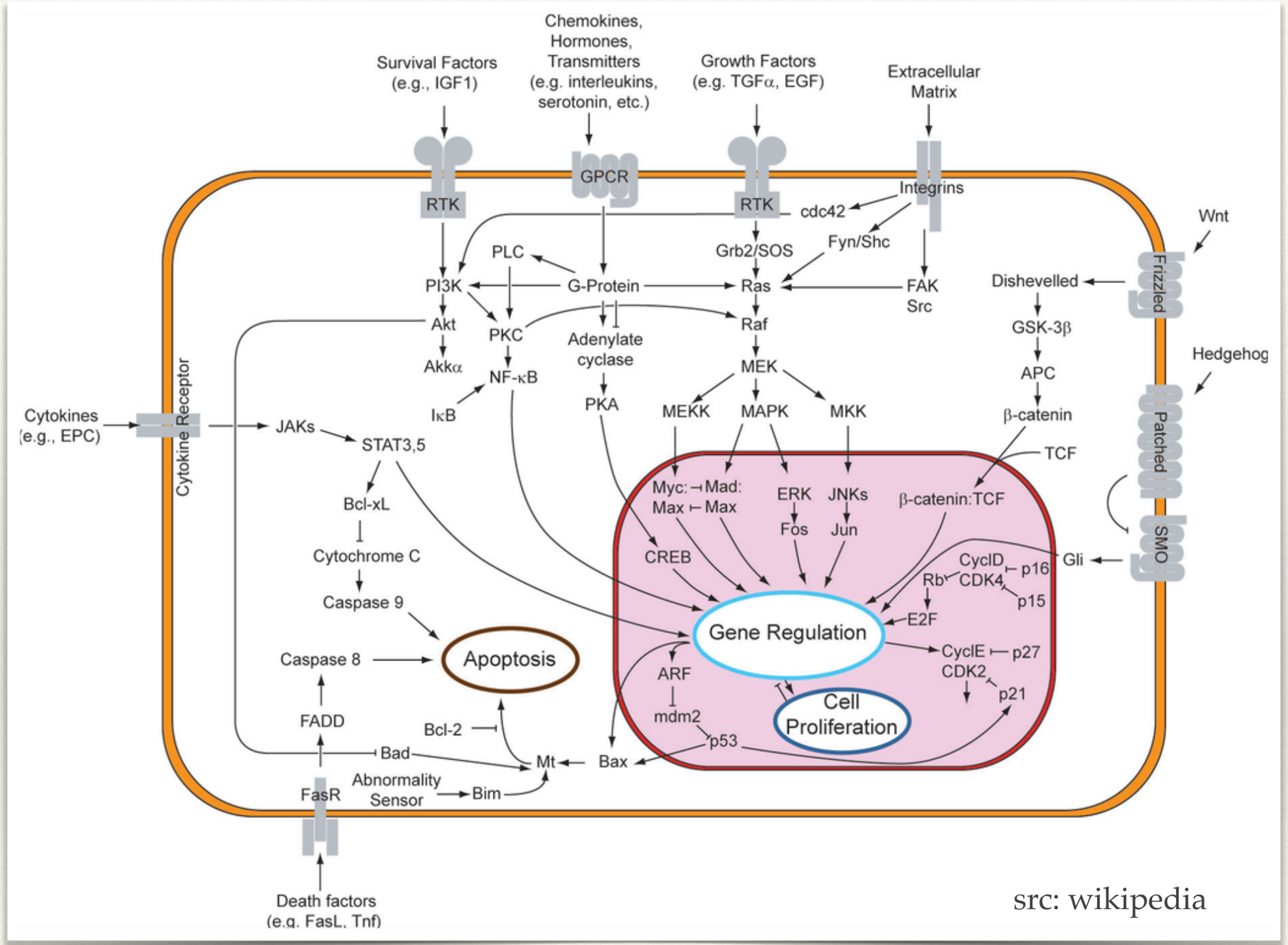
Logics as Knowledge assembly code for Molecular Biology

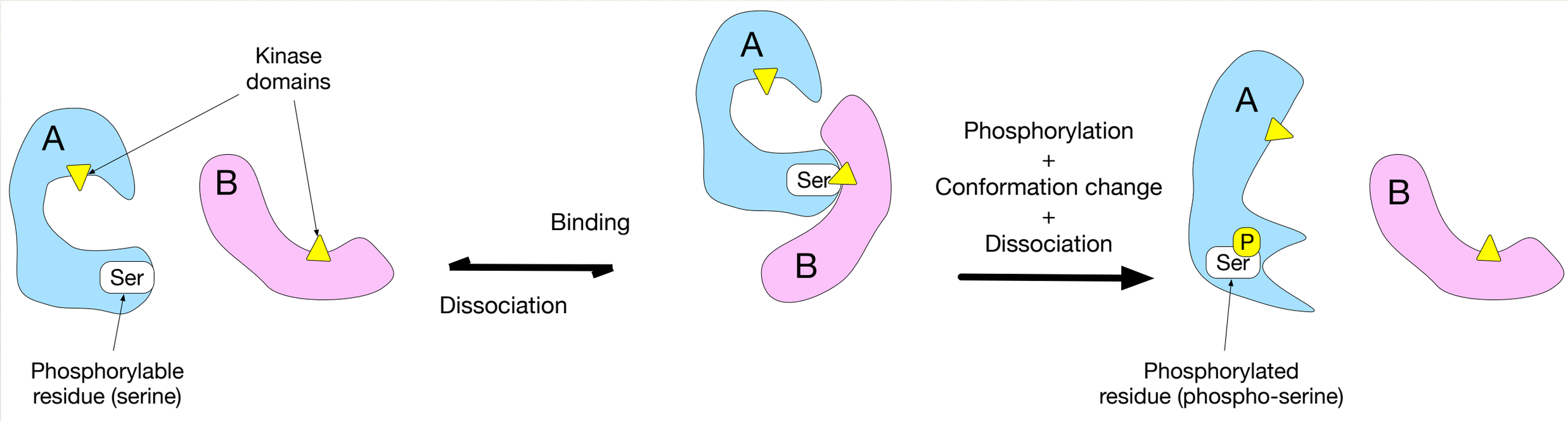
Jean Krivine

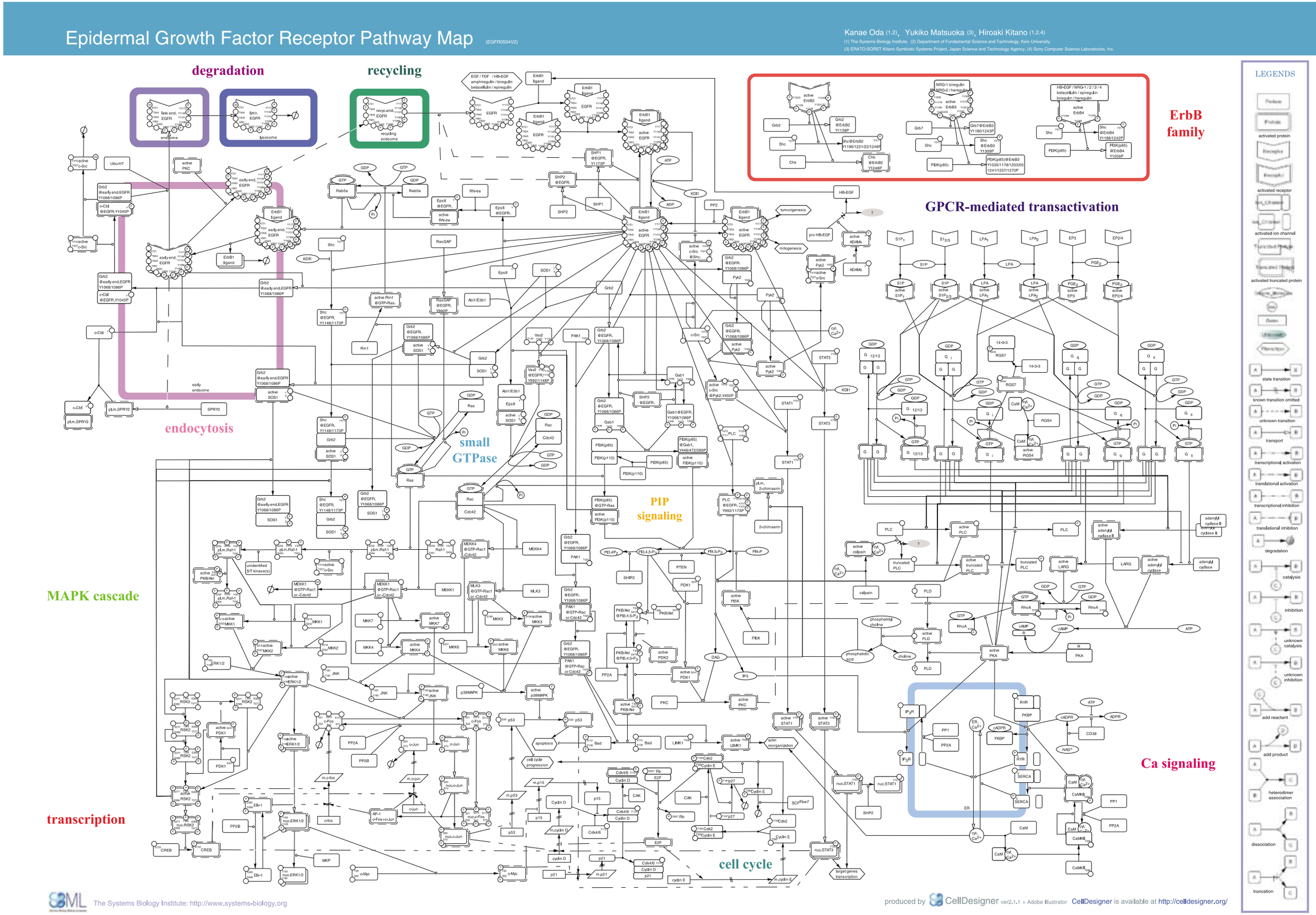


src: wikipedia

Cancer as abnormal signaling pathways

Elementary bricks





src: A Comprehensive pathway map of epidermal growth factor receptor signaling. Kitano et al. 2005

The language of molecular biologists

Since both S338 and Y341 phosphorylations are required for activation of Raf-1, it is interesting to consider how B-Raf is activated. Unlike Raf-1, B-Raf does not require tyrosine phosphorylation for activation, and does not have tyrosines at the positions equivalent to Y340/341 of Raf-1; in B-Raf, aspartates occupy these positions (D447 and D448; Figure 6A). These acidic residues seem to regulate some aspect of B-Raf activity since replacing them with phenylalanine or alanine reduces B-Raf activation by Ras (Figure 6; Marais *et al*., 1997). S445 in B-Raf is equivalent to S338 in Raf-1 and we have shown S445 to be phosphorylated. However, unlike Raf-1, phosphorylation at S445 in B-Raf is constitutive and if stimulated by Ras, the effect is small. Furthermore, whereas mutation of S338 of Raf-1 to alanine destroys its ability to be activated, mutation of S445 in B-Raf still permits a degree of activation. The striking effect of the S445 and D447/448 substitutions in B-Raf is the reduction they cause in basal kinase activity (Figure 6), which is normally 15–20 times higher than that of an equivalent amount of Raf-1 (Marais *et al*., 1997). Thus phosphorylation at S445 and the aspartic acids at positions 447/448 are responsible for the high basal kinase activity of B-Raf. However, phosphorylation at S445 is required for maximal B-Raf activity since the activity of B-Raf will be determined both by basal kinase activity and stimulation by Ras.

Although phosphorylation of S338 and Y341 in the N-region of Raf-1 is Ras dependent, Ras has at least one other role in Raf-1 activation. When S338 and Y341 are replaced with aspartic acid residues to mimic phosphorylation Ras still activates the substituted kinase (C.S.Mason and R.Marais, unpublished data). In effect these aspartic acid substitutions in Raf-1 mimic the situation in B-Raf and like B-Raf, Raf-1 with aspartic acid residues substituted for S338 or Y341 has high basal kinase activity (Marais *et al*., 1995; Diaz *et al*., 1997). Thus we propose that negative charge in the N-region has a permissive role to provide the correct alignment of residues within the kinase domain so that when Raf-1 interacts with Ras-GTP, the kinase can be activated. It is not clear how the interaction with Ras elevates Raf-1 activity; it may depend on membrane recruitment since Ras has only a small effect on the activation of membrane-bound RafCAAX (Marais *et al*., 1995). This membrane-associated event may be phosphorylation independent as postulated by Stokoe and McCormick and involve lipid interactions with Raf, possibly within the cysteine-rich domain, or within the catalytic domain (Ghosh *et al*., 1994; Mott *et al*., 1996; Stokoe and McCormick, 1997).

The language of molecular biologists

As for betacoronavirus, the N protein of SARS-CoV can be phosphorylated by multiple host kinases, including cyclin-dependent kinase, glycogen synthase kinase, mitogen-activated protein kinase and casein kinase II [129]. Using mass spectrometry analysis, six phosphorylation sites (S162, S170, T177, S389, S424 and T428) on the MHV-A59 N protein were identified [130]. Phosphorylation of the N protein of SARS-CoV and MHV-JHM by the host protein GSK-3 was precisely mapped to S197 and S177 in the serine arginine-rich region, respectively [131]. Moreover, inhibition of GSK-3 by kenpaullone significantly reduced the phosphorylation level of N protein, as well as the supernatant virus titer and cytopathic effects on VeroE6 cell-infected SARS-CoV [131]. Therefore, phosphorylation of the N protein appears to be essential for the replication of some *Betacoronaviruses*. In fact, a recent study showed that phosphorylation of the MHV-JHM N protein by GSK-3 allowed the recruitment of RNA helicase DDX1 to facilitate template read-through, enabling the synthesis of genomic RNA and longer sgRNAs [132]. On the other hand, when N protein was not phosphorylated, template switching was favored during transcription, leading to the preferential generation of shorter sgRNAs but not genomic RNA or longer sgRNAs [132]. Therefore, the phosphorylation status of MHV-JHM N protein acts as a switch to regulate the process of genome replication/transcription.

Controversies

Thus, another contradiction exists. In the proposed model, Pak3 is the kinase that mediates Ras-stimulated S338 phosphorylation through P13-K and Cdc42/Rac (49). It is therefore difficult to explain why Pak3, which is directly activated by V12Cdc42, phosphorylates Raf-1 in the cytosol, whereas when Ras activates Pak3 indirectly in a P13K/Cdc42-dependent manner, it is able to phosphorylate only membrane-bound Raf-1.

Implicit models lead to « functionalism »

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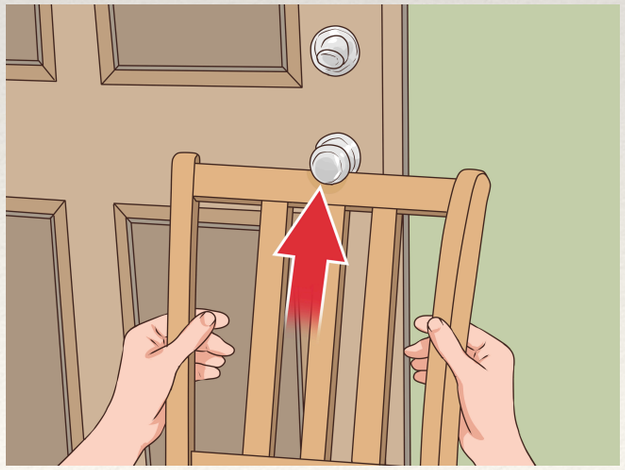
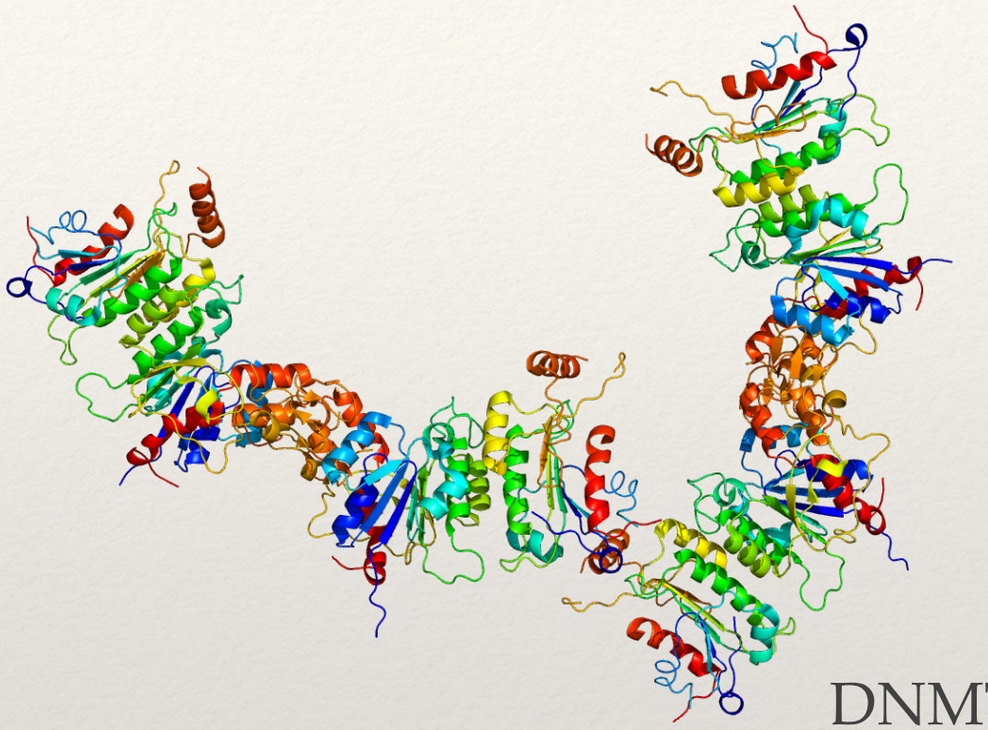
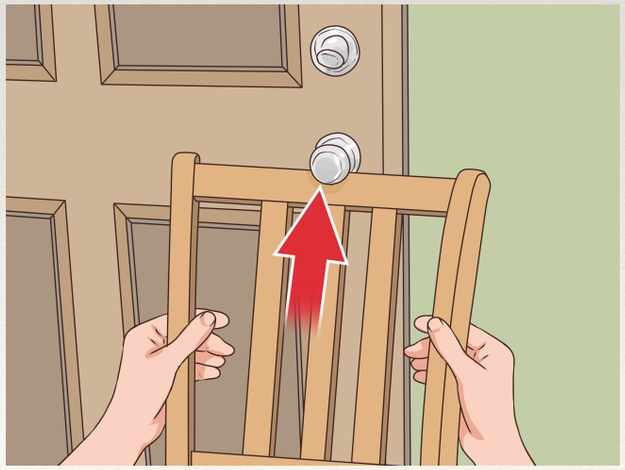


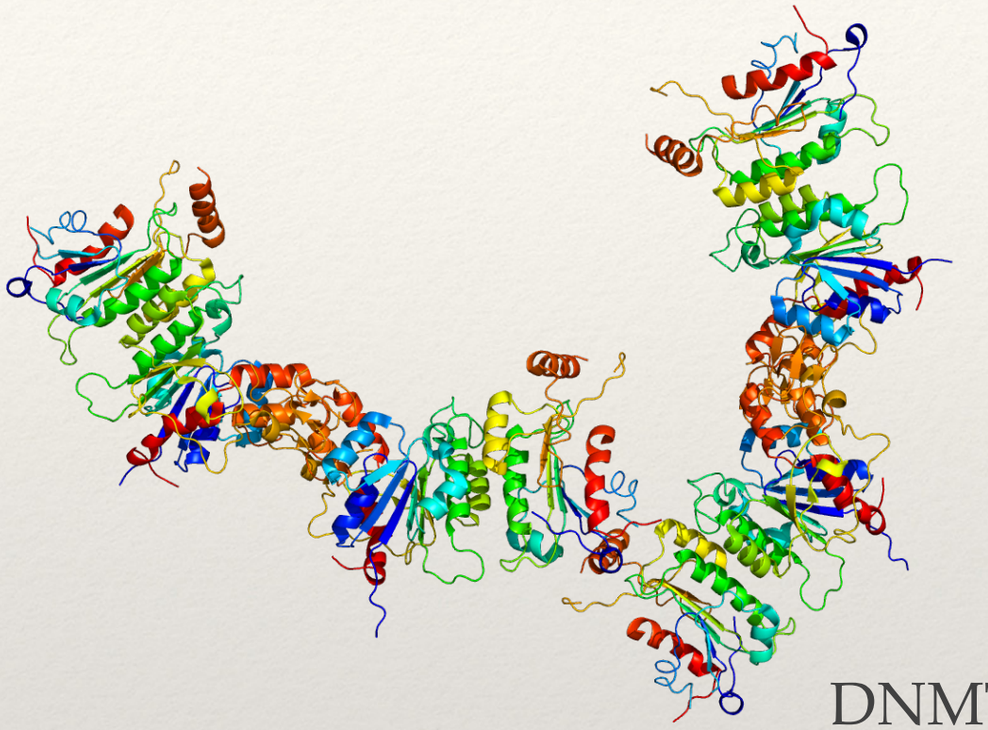
Implicit models lead to « functionalism »



DNMT3
src: wikipedia



Implicit models lead to « functionalism »



DNMT3
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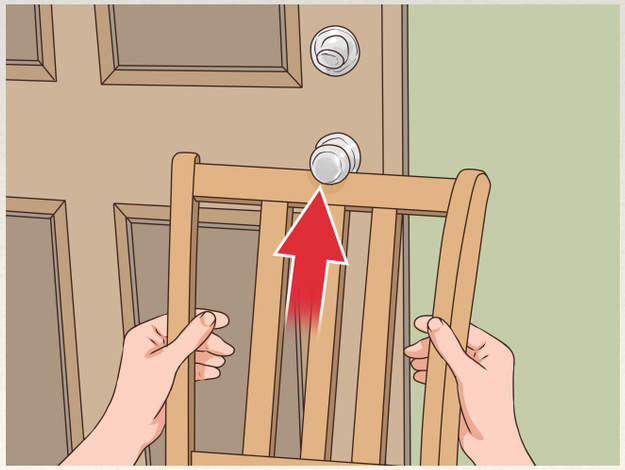


Biochim Biophys Acta Gene Regul Mech. 2018 Nov;1861(11):1048-1061. doi: 10.1016/j.bbagrm.2018.09.009. Epub 2018 Oct 6.

DNA Demethylation by DNMT3A and DNMT3B in vitro and of Methylated Episomal DNA in Transiently Transfected Cells.

Executable knowledge

Language and execution

$\texttt{fact} : Nat \rightarrow Nat$

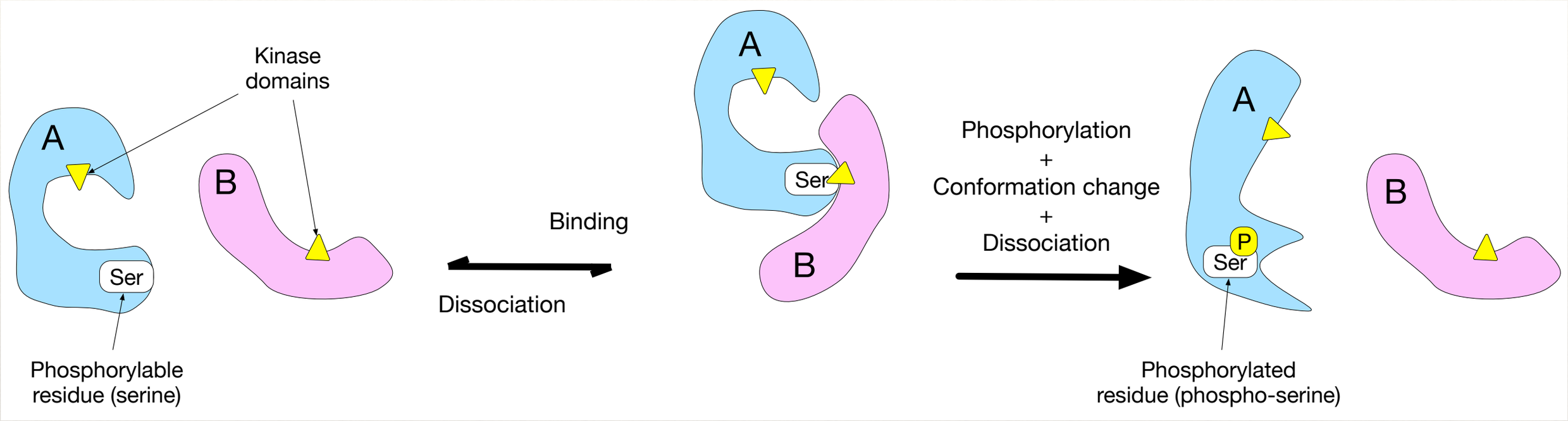
```
let rec fact(n) =
    if n = 0 then 1
    else n*fact(n-1)
```

```
.L102:
    movq    caml_afl_area_ptr@GOTPCREL(%rip), %rbx
    movq    (%rbx), %rdi
    movq    caml_afl_prev_loc@GOTPCREL(%rip), %rsi
    movq    (%rsi), %rdx
    xorq    $14493, %rdx
    movzbq  (%rdi,%rdx), %rcx
    incq    %rcx
    movb    %cl, (%rdi,%rdx)
    movq    $7246, (%rsi)
    cmpq    $3, %rax
    jg  .L101
    movq    (%rbx), %rax
    movq    (%rsi), %rbx
    xorq    $26649, %rbx
    movzbq  (%rax,%rbx), %rdi
    incq    %rdi
    movb    %dil, (%rax,%rbx)
    movq    $13324, (%rsi)
    movq    $3, %rax
    addq    $8, %rsp
    .cfi_adjust_cfa_offset -8
    ret
    .cfi_adjust_cfa_offset 8
    .align  4
```

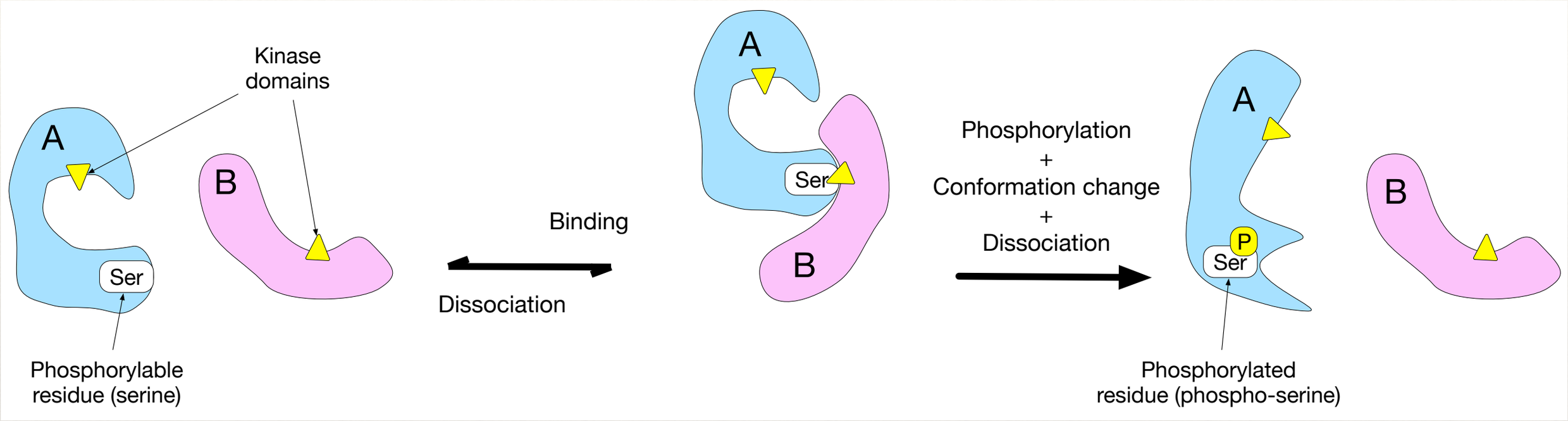
(Executable) **Knowledge**

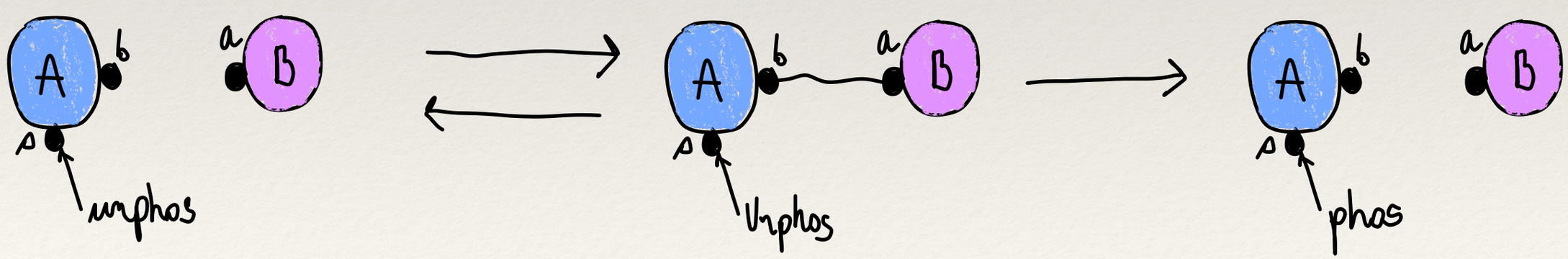
Executable (Knowledge)

The cell as a graph



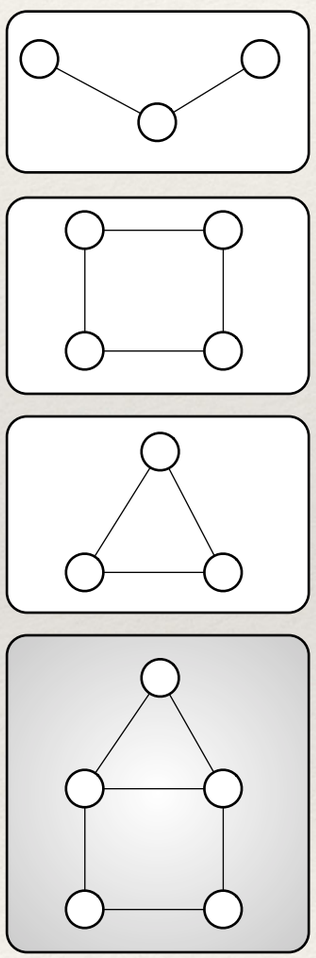
The cell as a graph

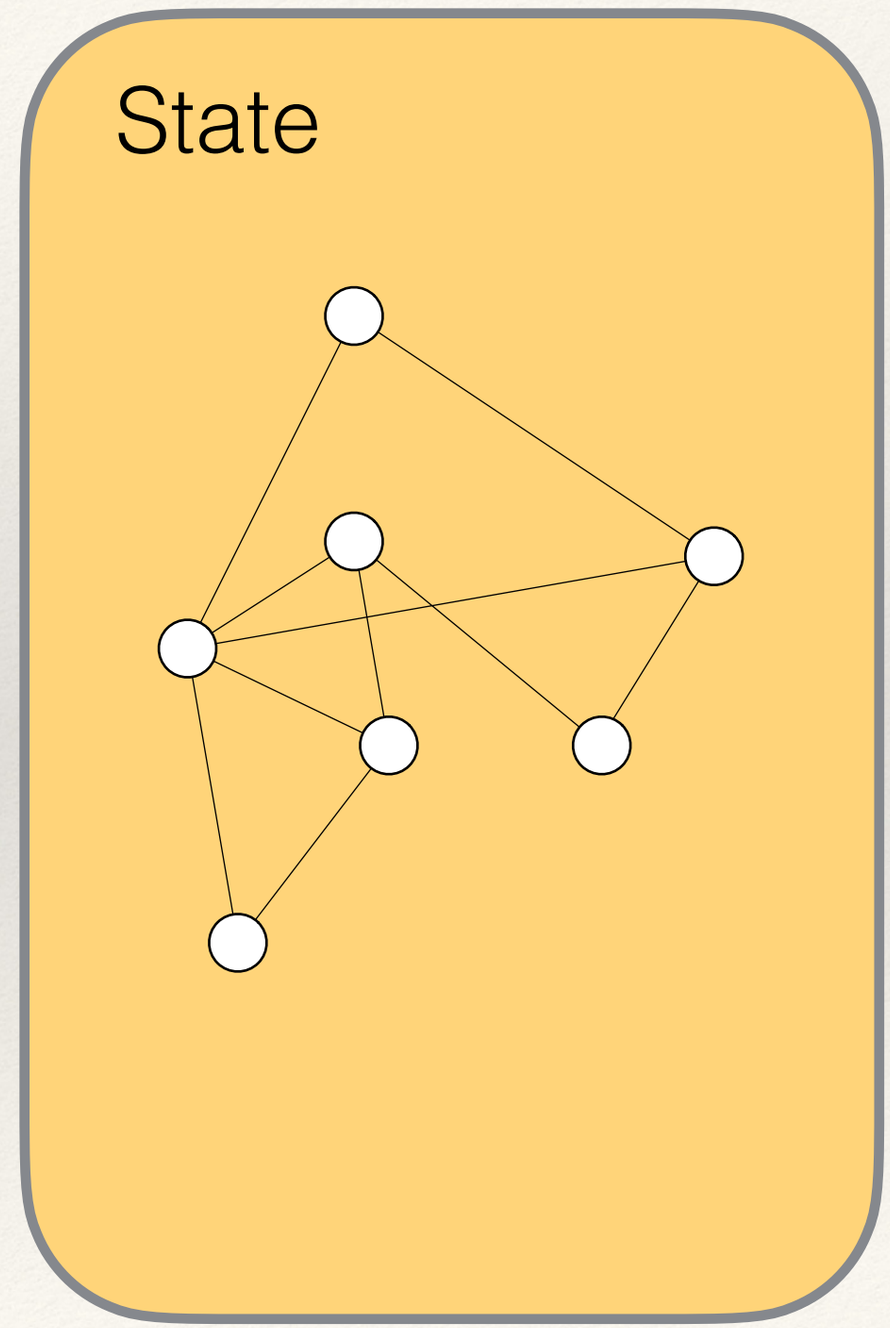




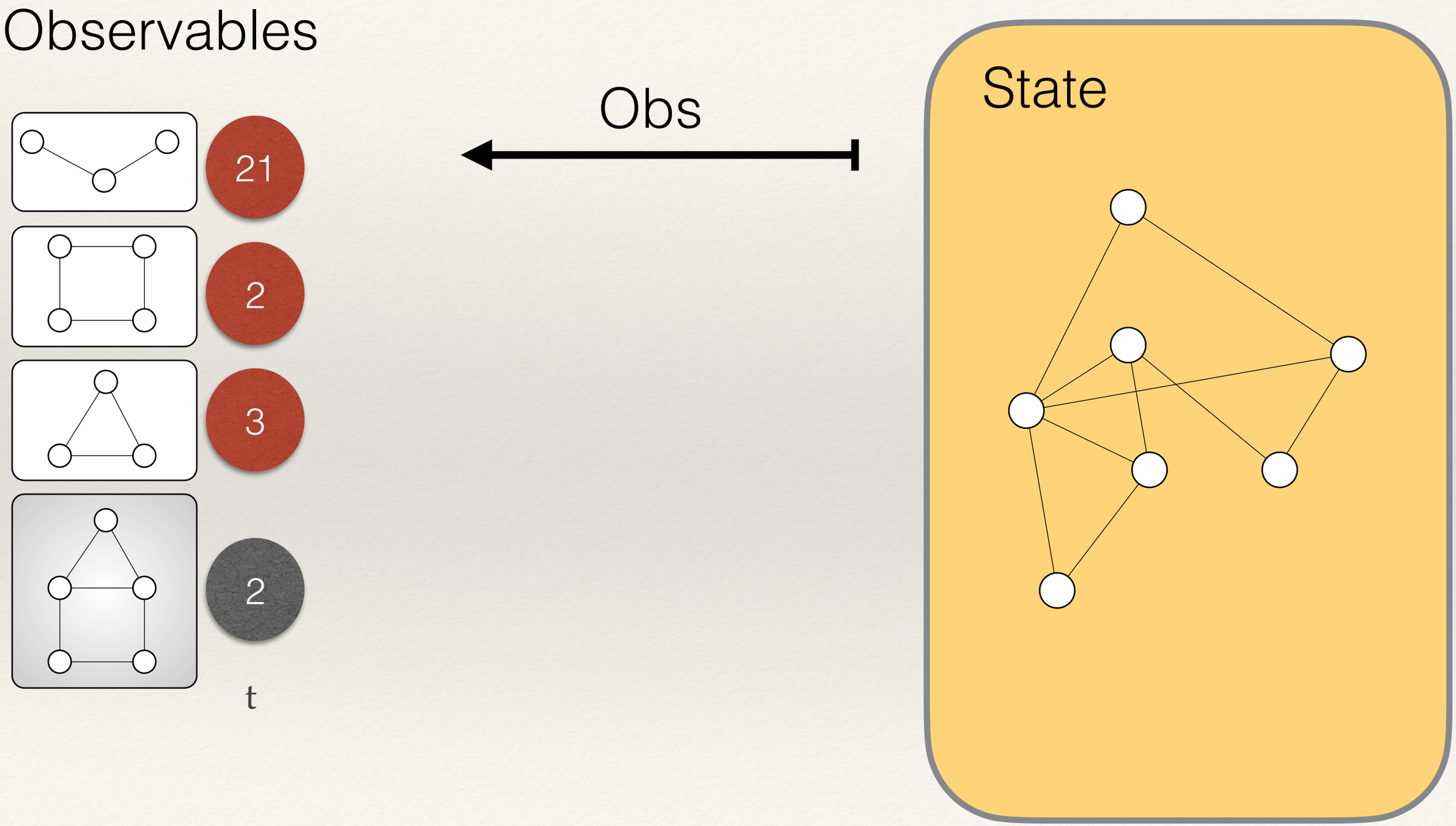
Execution

Observables



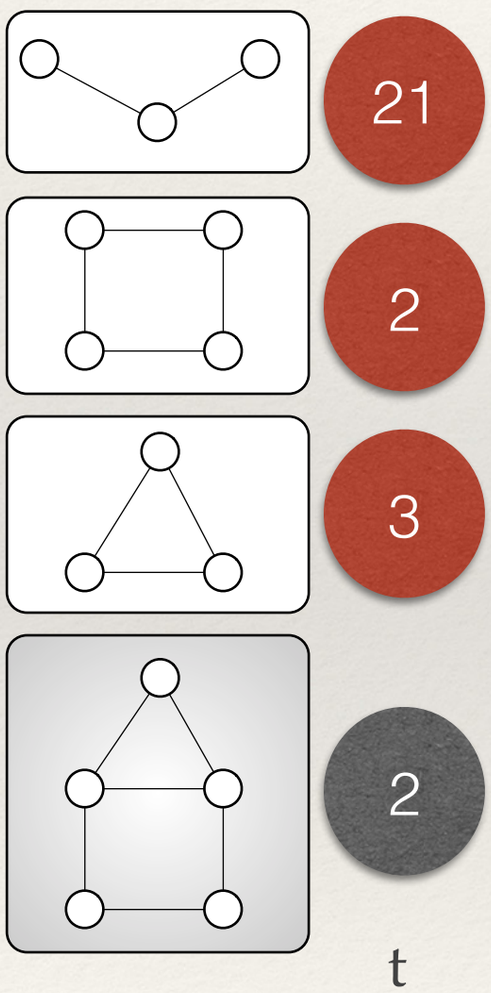


Execution



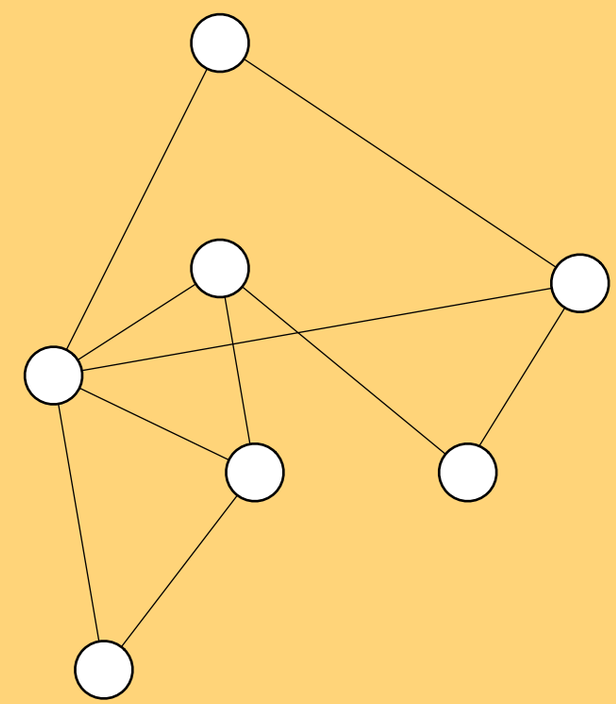
Execution

Observables



Obs

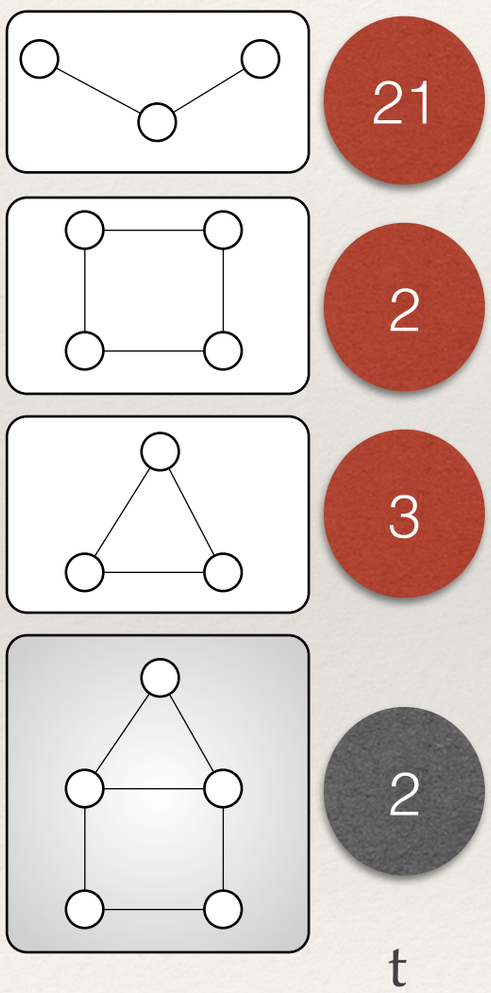
State

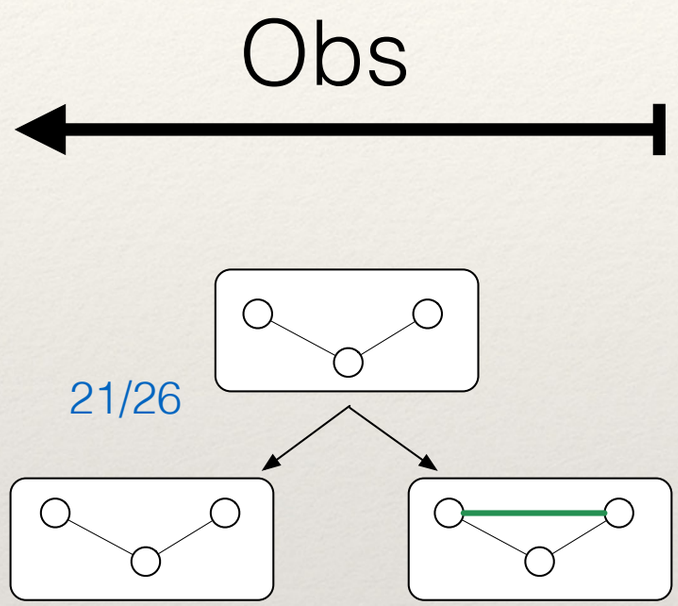


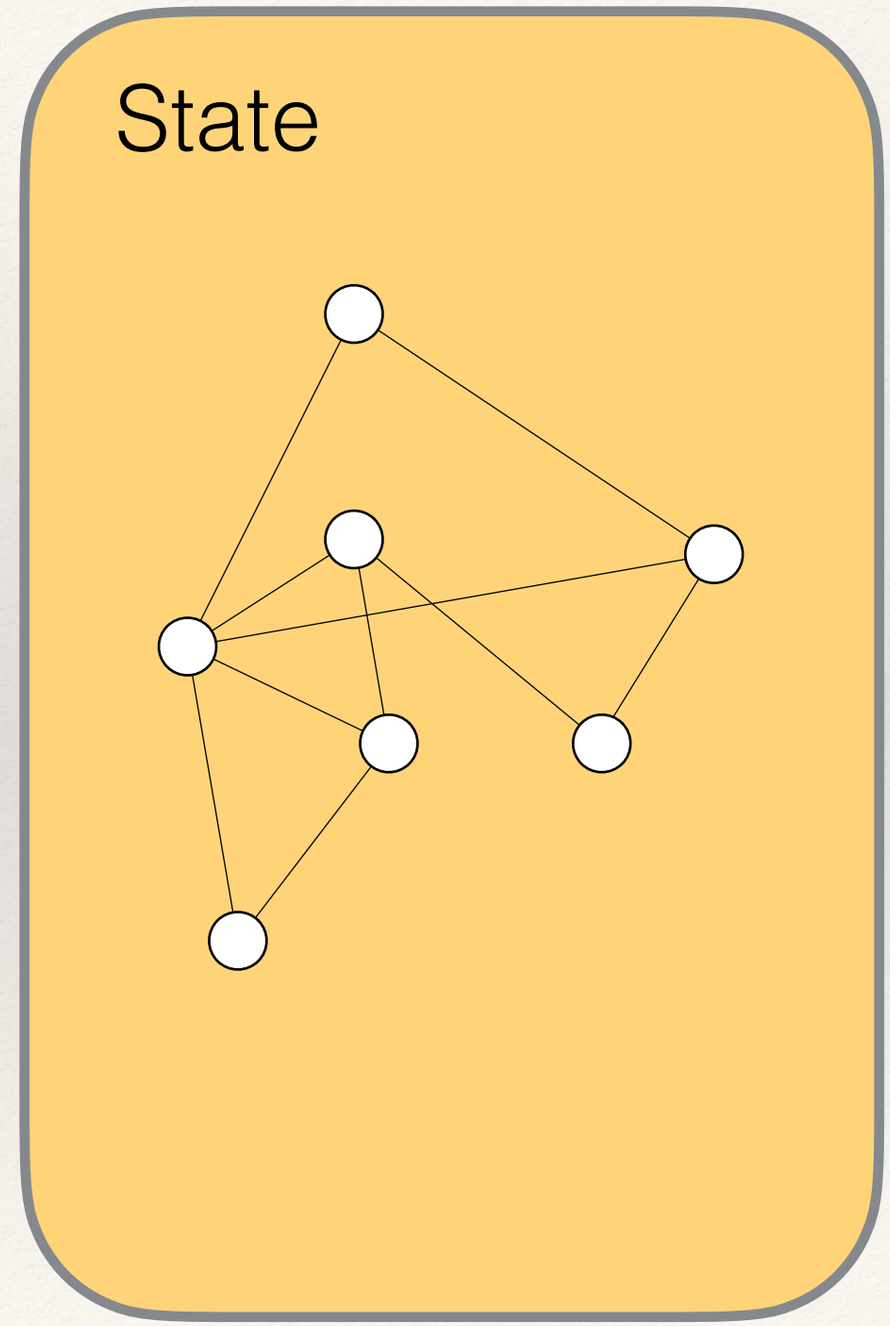
$$dt = \text{sample}[-26e^{-26t}] \sim \frac{1}{26}s$$

Execution

Observables

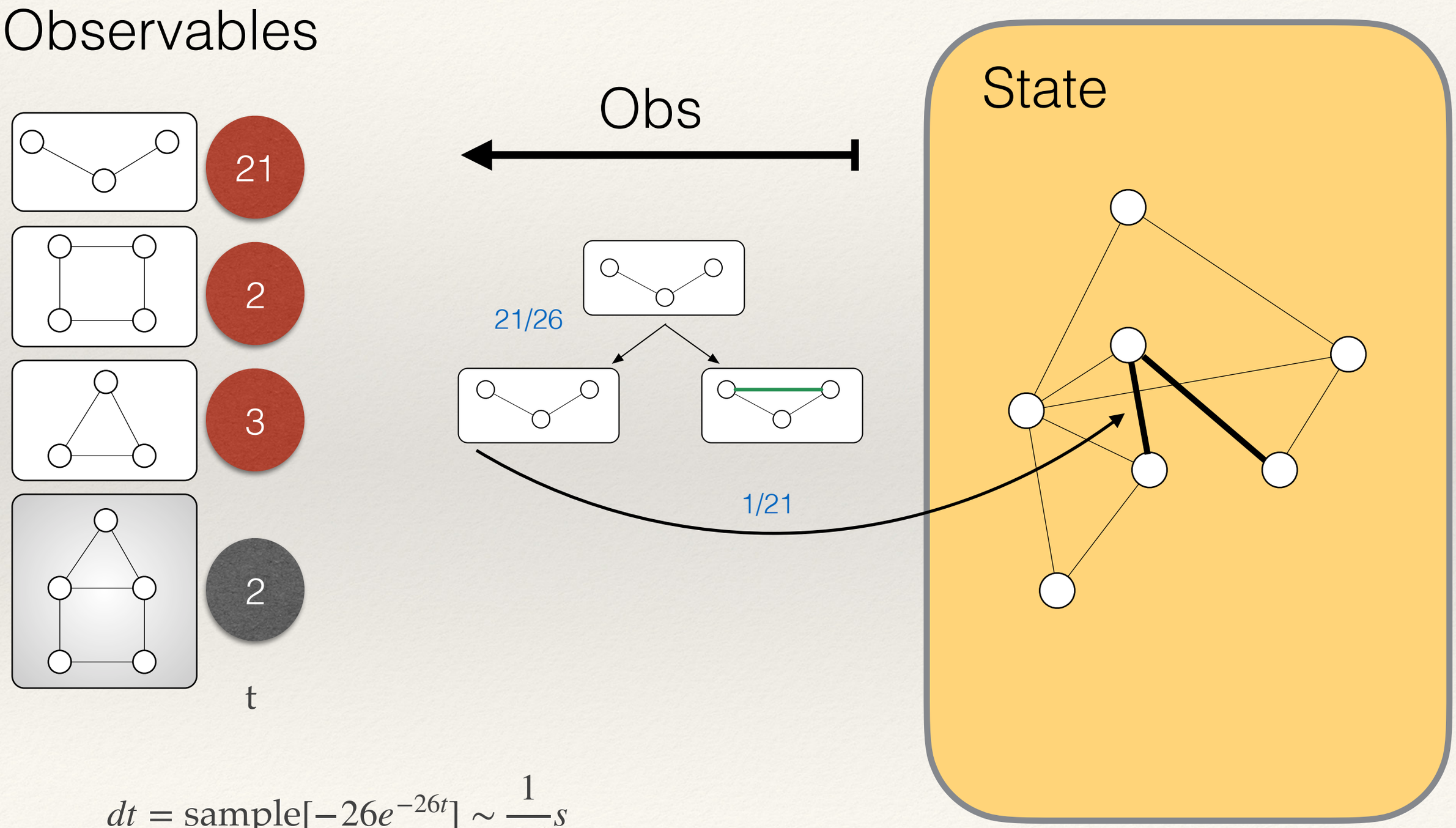






$$dt = \text{sample}[-26e^{-26t}] \sim \frac{1}{26}s$$

Execution



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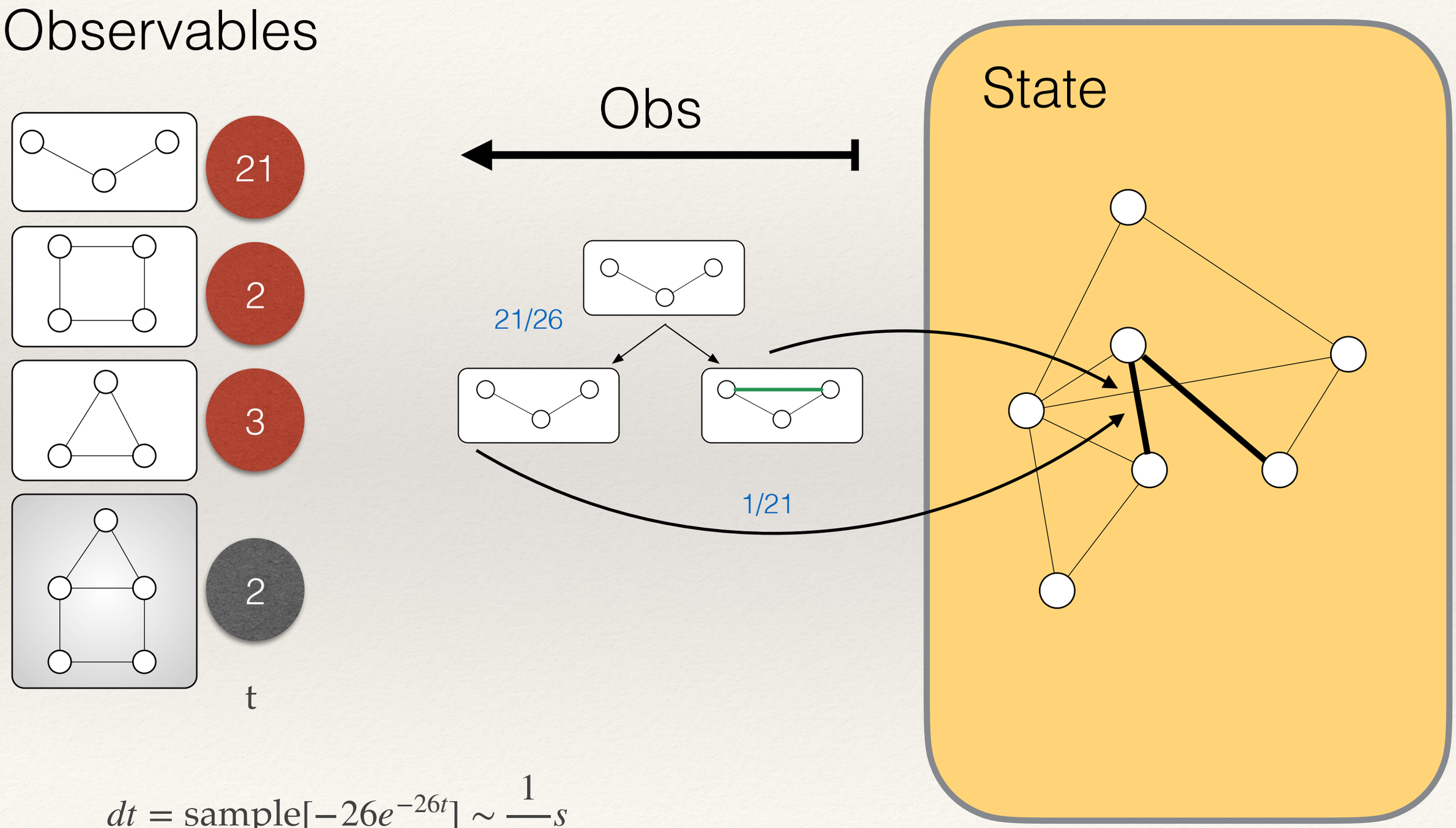
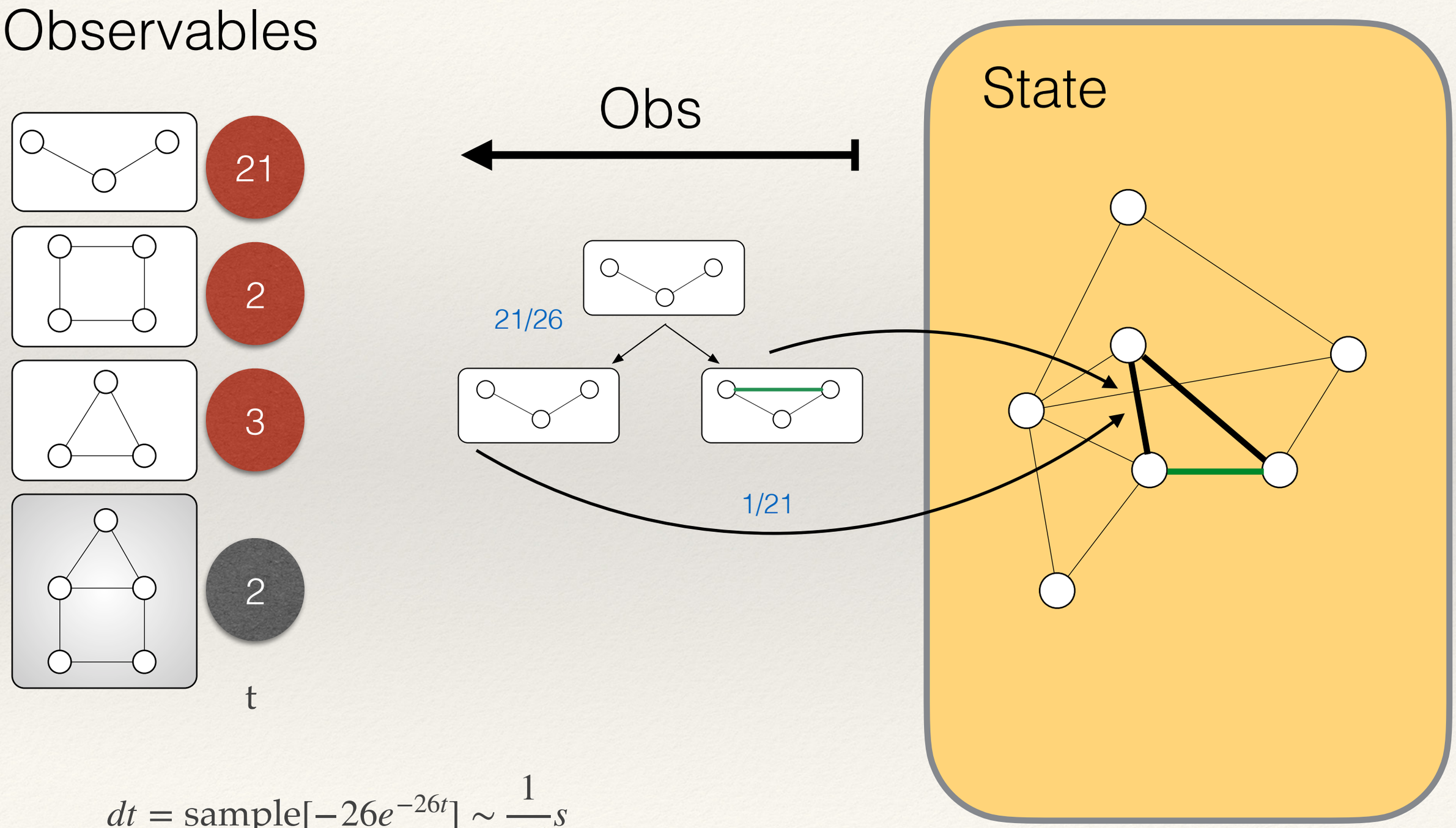
Execution



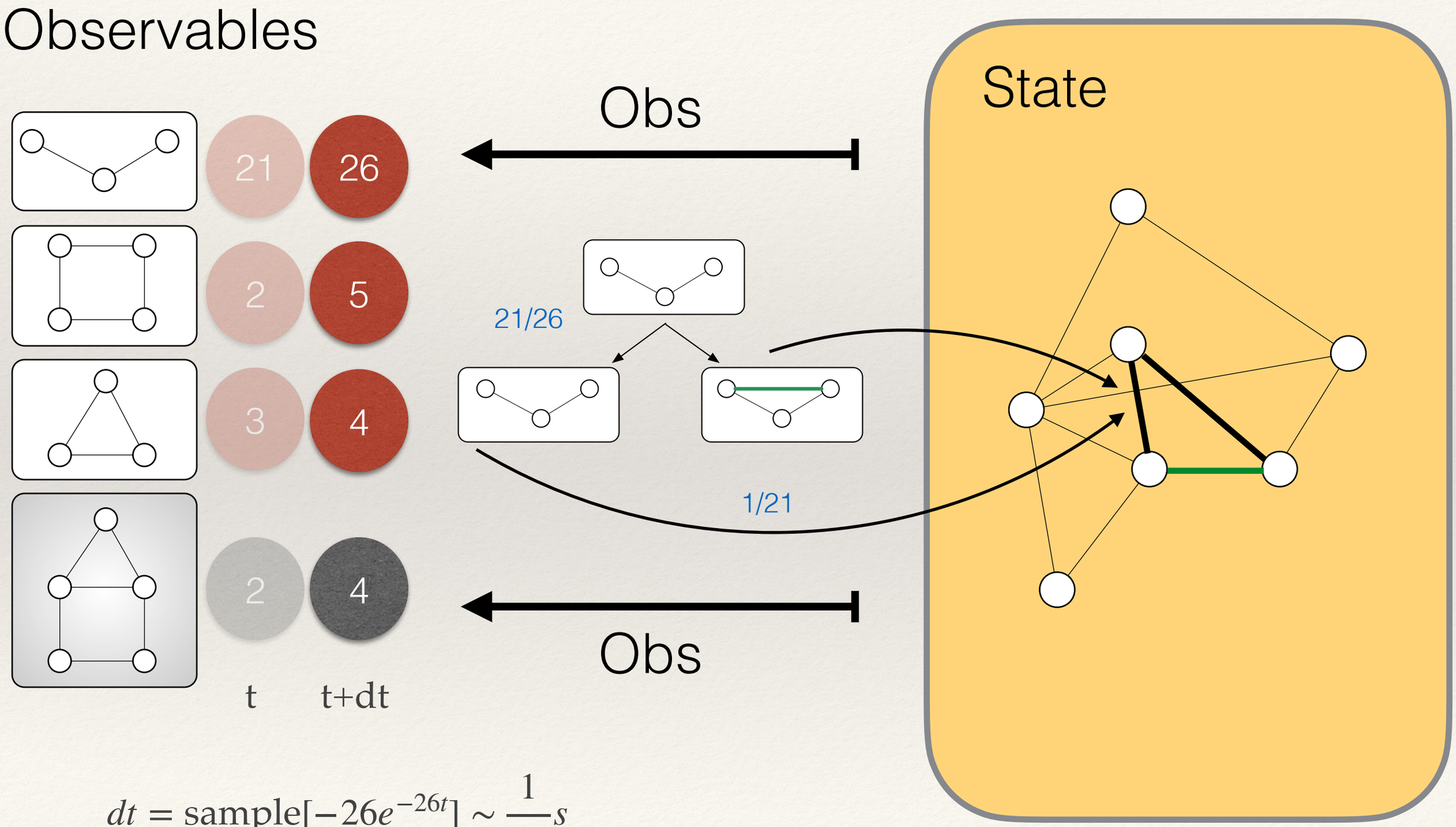
$$dt = \text{sample}[-26e^{-26t}] \sim \frac{1}{26}s$$

Execution



$$dt = \text{sample}[-26e^{-26t}] \sim \frac{1}{26}s$$

Execution



$$dt = \text{sample}[-26e^{-26t}] \sim \frac{1}{26}s$$

Knowledge as reverse engineering…

```
/*'EGFR.EGFR'
  EGFR(L[_],CR[.],N[.],C[.]), EGFR(L[_],CR,[.]N[.],C[.]) ->
  EGFR(L[_],CR[1],N[.],C[.]), EGFR(L[_],CR[1],N[.],C[.]) @ 'k_on'/2*/
'EGFR.EGFR'
  EGF(r[2]), EGFR(L[2],CR[.],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[.],N[.],C[.]) ->
  EGF(r[2]), EGFR(L[2],CR[1],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[1],N[.],C[.]) @
'k_on'/2

/*'EGFR/EGFR' EGFR(L!_,CR!1,N,C), EGFR(L!_,CR!1,N,C) -> EGFR(L!_,CR,N,C),
EGFR(L!_,CR,N,C) @ 'k_off'/2*/
/*'EGFR/EGFR' EGFR(CR!1,N,C), EGFR(CR!1,N,C) -> EGFR(CR,N,C), EGFR(CR,N,C) @
'k_off'/2*/
'EGFR/EGFR'
  EGF(r[2]), EGFR(L[2],CR[1],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[1],N[.],C[.]) ->
  EGF(r[2]), EGFR(L[2],CR[.],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[.],N[.],C[.]) @
'k_off'/2

'EGF.EGFR' EGF(r[.]), EGFR(L[.],CR[.]) -> EGF(r[1]), EGFR(L[1],CR[.]) @ 'k_on'
'EGF/EGFR' EGF(r[1]), EGFR(L[1],CR[.]) -> EGF(r[.]), EGFR(L[.],CR[.]) @ 'k_off'
'Shc.Grb2' Shc(Y[.]{p}), Grb2(SH2[.]) -> Shc(Y[1]{p}), Grb2(SH2[1]) @ 5*'k_on'
'Shc/Grb2' Shc(Y{p}[1]), Grb2(SH2[1]) -> Shc(Y{p}[.]), Grb2(SH2[.]) @ 'k_off'
'EGFR.Grb2' EGFR(Y1092{p}[.]), Grb2(SH2[.]) -> EGFR(Y1092{p}[1]), Grb2(SH2[1]) @
'k_on'
'EGFR/Grb2' EGFR(Y1092{p}[1]), Grb2(SH2[1]) -> EGFR(Y1092{p}[.]), Grb2(SH2[.]) @
'k_off'
'EGFR.Shc' EGFR(Y1172{p}[.]), Shc(PTB[.]) -> EGFR(Y1172{p}[1]), Shc(PTB[1]) @
'k_on'
'EGFR/Shc' EGFR(Y1172{p}[1]), Shc(PTB[1]) -> EGFR(Y1172{p}[.]), Shc(PTB[.]) @
'k_off'
'Grb2.SoS' Grb2(SH3n[.]), SoS(PR[.],S[.]{u}) -> Grb2(SH3n[1]), SoS(PR[1],S[.]{u})
@ 'k_on'
'Grb2/SoS' Grb2(SH3n[1]), SoS(PR[1]) -> Grb2(SH3n[.]), SoS(PR[.]) @ 'k_off'
'EGFR.int' EGFR(CR[1],N[.],C[.]), EGFR(CR[1],N[.],C[.]) -> EGFR(CR[1],N[2],C[.]),
EGFR(CR[1],N[.],C[2]) @ 'k_on'
'EGFR/int' EGFR(CR[1],N[2],C[.]), EGFR(CR[1],N[.],C[2]) -> EGFR(CR[1],N[.],C[.]),
EGFR(CR[1],N[.],C[.]) @ 'k_off'
'pY1092@EGFR' EGFR(N[1]), EGFR(C[1],Y1092{u}[.]) -> EGFR(N[1]), EGFR(C[1],Y1092{p}
[.]) @ 'k_cat'
'pY1172@EGFR' EGFR(N[1]), EGFR(C[1],Y1172[.]{u}) -> EGFR(N[1]), EGFR(C[1],Y1172[.]
{p}) @ 'k_cat'
'uY1092@EGFR' EGFR(Y1092[.]{p}) -> EGFR(Y1092[.]{u}) @ 'k_cat'
'uY1172@EGFR' EGFR(Y1172{p}[.]) -> EGFR(Y1172{u}[.]) @ 'k_cat'
```

One needs to document rules
to relate them to knowledge

Knowledge as reverse engineering…

```
'EGF.EGFR' EGF(r[.]), EGFR(L[.],CR[.]) -> EGF(r[1]), EGFR(L[1],CR[.]) @ 'k_on'
'EGF/EGFR' EGF(r[1]), EGFR(L[1],CR[.]) -> EGF(r[.]), EGFR(L[.],CR[.]) @ 'k_off'
```

```
  EGF(r[2]), EGFR(L[2],CR[1],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[1],N[.],C[.]) @
'k_on'/2

/*'EGFR/EGFR' EGFR(L!_,CR!1,N,C), EGFR(L!_,CR!1,N,C) -> EGFR(L!_,CR,N,C),
EGFR(L!_,CR,N,C) @ 'k_off'/2*/
/*'EGFR/EGFR' EGFR(CR!1,N,C), EGFR(CR!1,N,C) -> EGFR(CR,N,C), EGFR(CR,N,C) @
'k_off'/2*/
'EGFR/EGFR'
  EGF(r[2]), EGFR(L[2],CR[1],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[1],N[.],C[.]) ->
  EGF(r[2]), EGFR(L[2],CR[.],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[.],N[.],C[.]) @
'k_off'/2

'EGF.EGFR' EGF(r[.]), EGFR(L[.],CR[.]) -> EGF(r[1]), EGFR(L[1],CR[.]) @ 'k_on'
'EGF/EGFR' EGF(r[1]), EGFR(L[1],CR[.]) -> EGF(r[.]), EGFR(L[.],CR[.]) @ 'k_off'
'Shc.Grb2' Shc(Y[.]{p}), Grb2(SH2[.]) -> Shc(Y[1]{p}), Grb2(SH2[1]) @ 5*'k_on'
'Shc/Grb2' Shc(Y{p}[1]), Grb2(SH2[1]) -> Shc(Y{p}[.]), Grb2(SH2[.]) @ 'k_off'
'EGFR.Grb2' EGFR(Y1092{p}[.]), Grb2(SH2[.]) -> EGFR(Y1092{p}[1]), Grb2(SH2[1]) @
'k_on'
'EGFR/Grb2' EGFR(Y1092{p}[1]), Grb2(SH2[1]) -> EGFR(Y1092{p}[.]), Grb2(SH2[.]) @
'k_off'
'EGFR.Shc' EGFR(Y1172{p}[.]), Shc(PTB[.]) -> EGFR(Y1172{p}[1]), Shc(PTB[1]) @
'k_on'
'EGFR/Shc' EGFR(Y1172{p}[1]), Shc(PTB[1]) -> EGFR(Y1172{p}[.]), Shc(PTB[.]) @
'k_off'
'Grb2.SoS' Grb2(SH3n[.]), SoS(PR[.],S[.]{u}) -> Grb2(SH3n[1]), SoS(PR[1],S[.]{u})
@ 'k_on'
'Grb2/SoS' Grb2(SH3n[1]), SoS(PR[1]) -> Grb2(SH3n[.]), SoS(PR[.]) @ 'k_off'
'EGFR.int' EGFR(CR[1],N[.],C[.]), EGFR(CR[1],N[.],C[.]) -> EGFR(CR[1],N[2],C[.]),
EGFR(CR[1],N[.],C[2]) @ 'k_on'
'EGFR/int' EGFR(CR[1],N[2],C[.]), EGFR(CR[1],N[.],C[2]) -> EGFR(CR[1],N[.],C[.]),
EGFR(CR[1],N[.],C[.]) @ 'k_off'
'pY1092@EGFR' EGFR(N[1]), EGFR(C[1],Y1092{u}[.]) -> EGFR(N[1]), EGFR(C[1],Y1092{p}
[.]) @ 'k_cat'
'pY1172@EGFR' EGFR(N[1]), EGFR(C[1],Y1172[.]{u}) -> EGFR(N[1]), EGFR(C[1],Y1172[.]
{p}) @ 'k_cat'
'uY1092@EGFR' EGFR(Y1092[.]{p}) -> EGFR(Y1092[.]{u}) @ 'k_cat'
'uY1172@EGFR' EGFR(Y1172{p}[.]) -> EGFR(Y1172{u}[.]) @ 'k_cat'
```

One needs to document rules
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Knowledge as reverse engineering…

```
'EGF.EGFR' EGF(r[.]), EGFR(L[.],CR[.]) -> EGF(r[1]), EGFR(L[1],CR[.]) @ 'k_on'
'EGF/EGFR' EGF(r[1]), EGFR(L[1],CR[.]) -> EGF(r[.]), EGFR(L[.],CR[.]) @ 'k_off'
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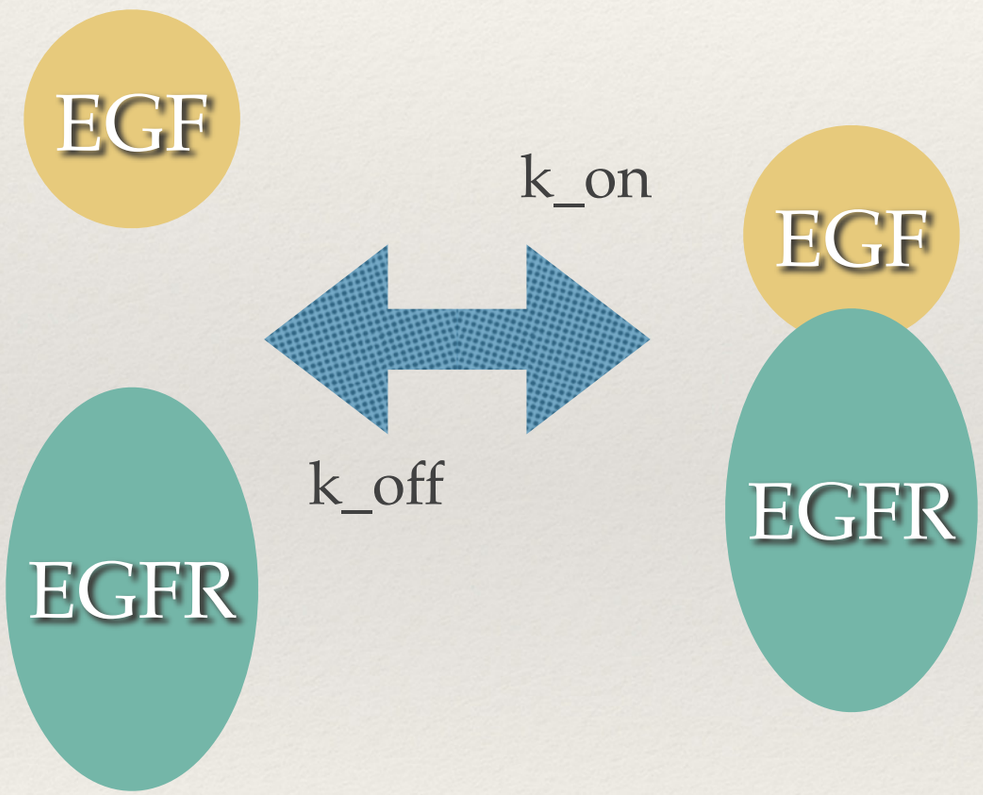


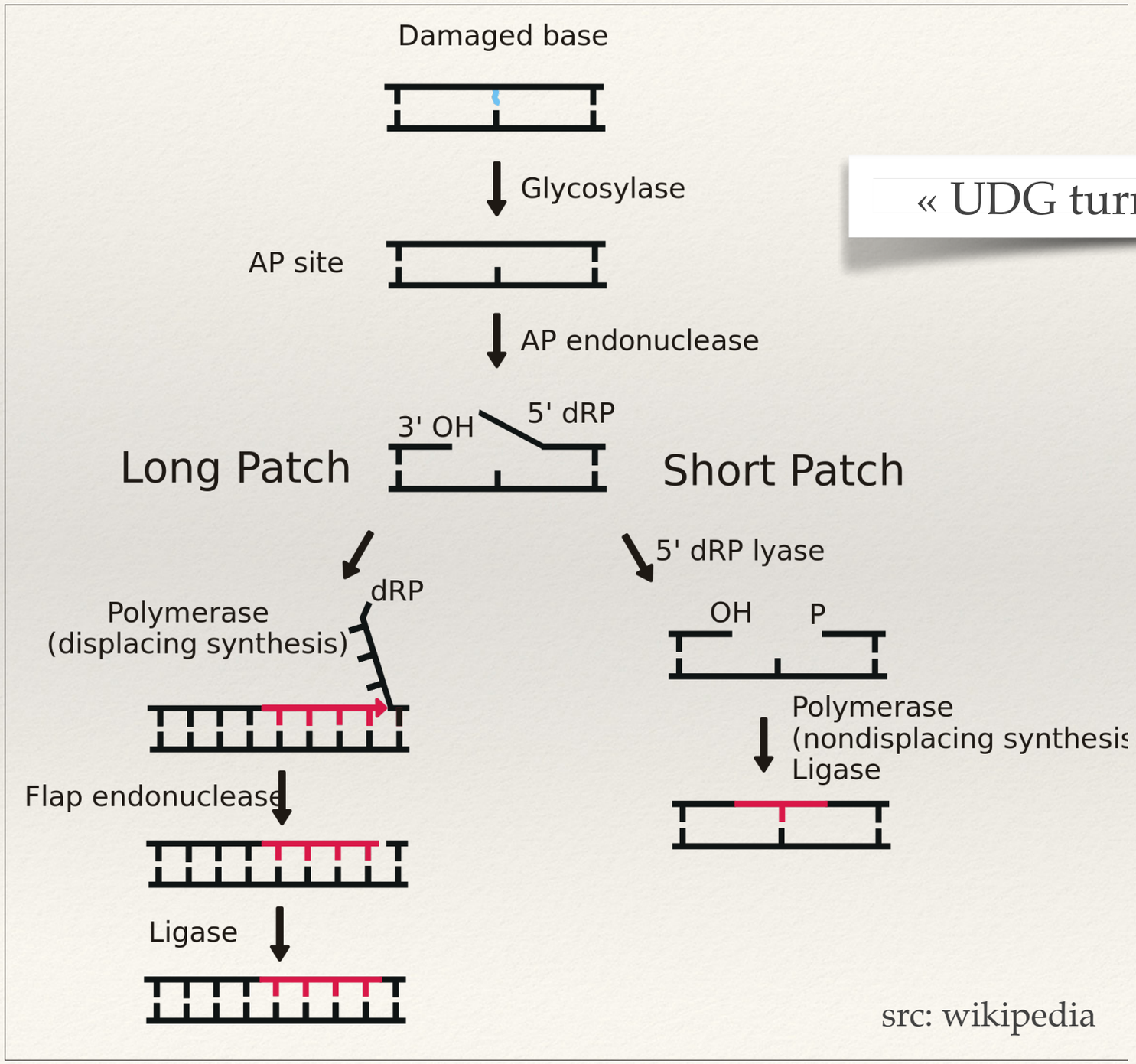
One needs to document rules
to relate them to knowledge

```
  EGF(r[2]), EGFR(L[2],CR[1],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[1],N[.],C[.]) @
'k_on'/2

/*'EGFR/EGFR' EGFR(L!_,CR!1,N,C), EGFR(L!_,CR!1,N,C) -> EGFR(L!_,CR,N,C),
EGFR(L!_,CR,N,C) @ 'k_off'/2*/
/*'EGFR/EGFR' EGFR(CR!1,N,C), EGFR(CR!1,N,C) -> EGFR(CR,N,C), EGFR(CR,N,C) @
'k_off'/2*/
'EGFR/EGFR'
  EGF(r[2]), EGFR(L[2],CR[1],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[1],N[.],C[.]) ->
  EGF(r[2]), EGFR(L[2],CR[.],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[.],N[.],C[.]) @
'k_off'/2

'EGF.EGFR' EGF(r[.]), EGFR(L[.],CR[.]) -> EGF(r[1]), EGFR(L[1],CR[.]) @ 'k_on'
'EGF/EGFR' EGF(r[1]), EGFR(L[1],CR[.]) -> EGF(r[.]), EGFR(L[.],CR[.]) @ 'k_off'
'Shc.Grb2' Shc(Y[.]{p}), Grb2(SH2[.]) -> Shc(Y[1]{p}), Grb2(SH2[1]) @ 5*'k_on'
'Shc/Grb2' Shc(Y{p}[1]), Grb2(SH2[1]) -> Shc(Y{p}[.]), Grb2(SH2[.]) @ 'k_off'
'EGFR.Grb2' EGFR(Y1092{p}[.]), Grb2(SH2[.]) -> EGFR(Y1092{p}[1]), Grb2(SH2[1]) @
'k_on'
'EGFR/Grb2' EGFR(Y1092{p}[1]), Grb2(SH2[1]) -> EGFR(Y1092{p}[.]), Grb2(SH2[.]) @
'k_off'
'EGFR.Shc' EGFR(Y1172{p}[.]), Shc(PTB[.]) -> EGFR(Y1172{p}[1]), Shc(PTB[1]) @
'k_on'
'EGFR/Shc' EGFR(Y1172{p}[1]), Shc(PTB[1]) -> EGFR(Y1172{p}[.]), Shc(PTB[.]) @
'k_off'
'Grb2.SoS' Grb2(SH3n[.]), SoS(PR[.],S[.]{u}) -> Grb2(SH3n[1]), SoS(PR[1],S[.]{u})
@ 'k_on'
'Grb2/SoS' Grb2(SH3n[1]), SoS(PR[1]) -> Grb2(SH3n[.]), SoS(PR[.]) @ 'k_off'
'EGFR.int' EGFR(CR[1],N[.],C[.]), EGFR(CR[1],N[.],C[.]) -> EGFR(CR[1],N[2],C[.]),
EGFR(CR[1],N[.],C[2]) @ 'k_on'
'EGFR/int' EGFR(CR[1],N[2],C[.]), EGFR(CR[1],N[.],C[2]) -> EGFR(CR[1],N[.],C[.]),
EGFR(CR[1],N[.],C[.]) @ 'k_off'
'pY1092@EGFR' EGFR(N[1]), EGFR(C[1],Y1092{u}[.]) -> EGFR(N[1]), EGFR(C[1],Y1092{p}
[.]) @ 'k_cat'
'pY1172@EGFR' EGFR(N[1]), EGFR(C[1],Y1172[.]{u}) -> EGFR(N[1]), EGFR(C[1],Y1172[.]
{p}) @ 'k_cat'
'uY1092@EGFR' EGFR(Y1092[.]{p}) -> EGFR(Y1092[.]{u}) @ 'k_cat'
'uY1172@EGFR' EGFR(Y1172{p}[.]) -> EGFR(Y1172{u}[.]) @ 'k_cat'
```

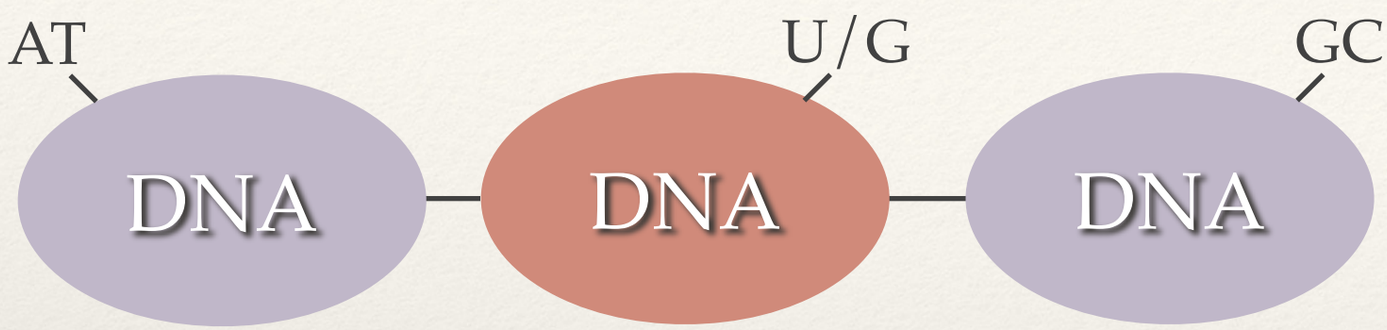
DNA repair example



« UDG turns U/G mismatch into AP/G »

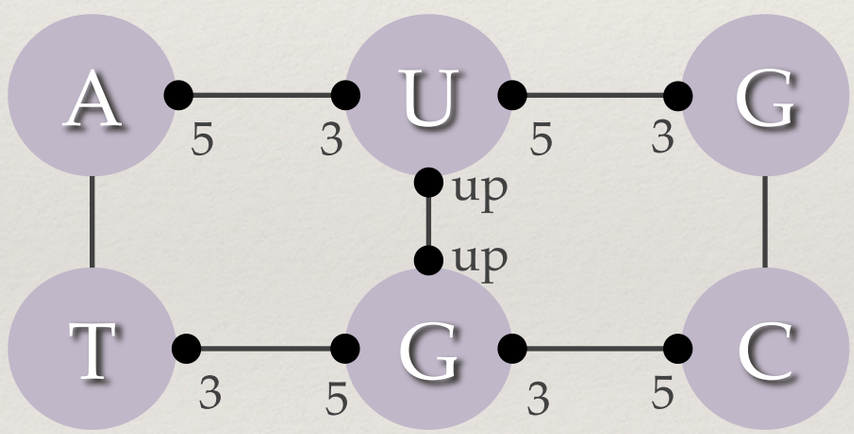
src: wikipedia

« Iota »



U/G : 1 a U/G mismatch in double strand DNA

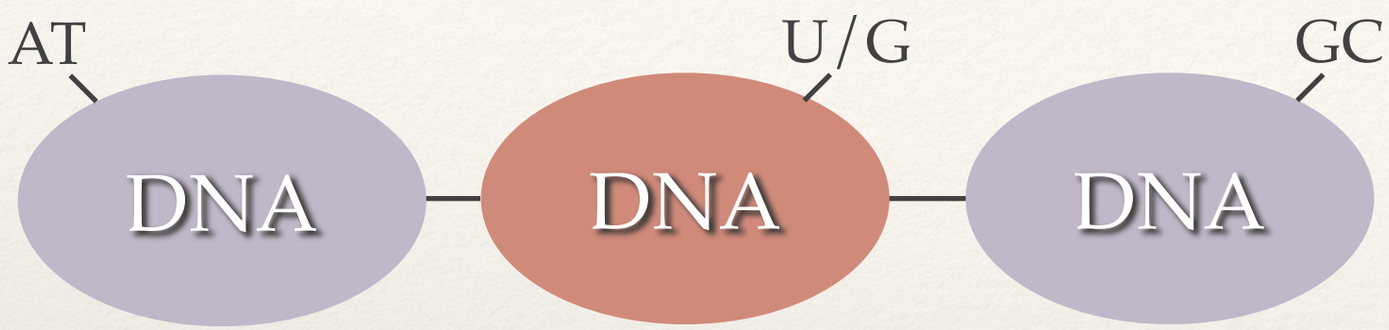
AP/G : 1 an AP/G site in double strand DNA



U/G : 2 a U/G mismatch in double strand DNA, U:1, G:1

AP/G : 1 an AP/G site in double strand DNA, G:1

« Iota »

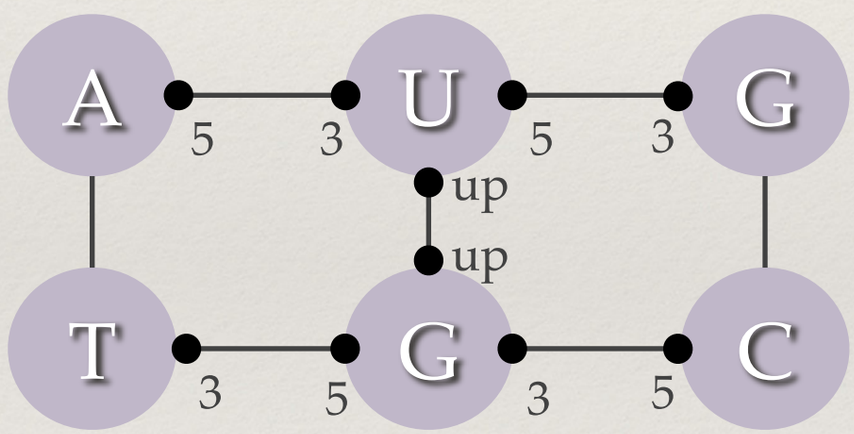


$U/G : 1$ a U/G mismatch in double strand DNA

$AP/G : 1$ an AP/G site in double strand DNA

$U/G(x) := \mathbf{DNA}(x) \wedge$ ● (x)

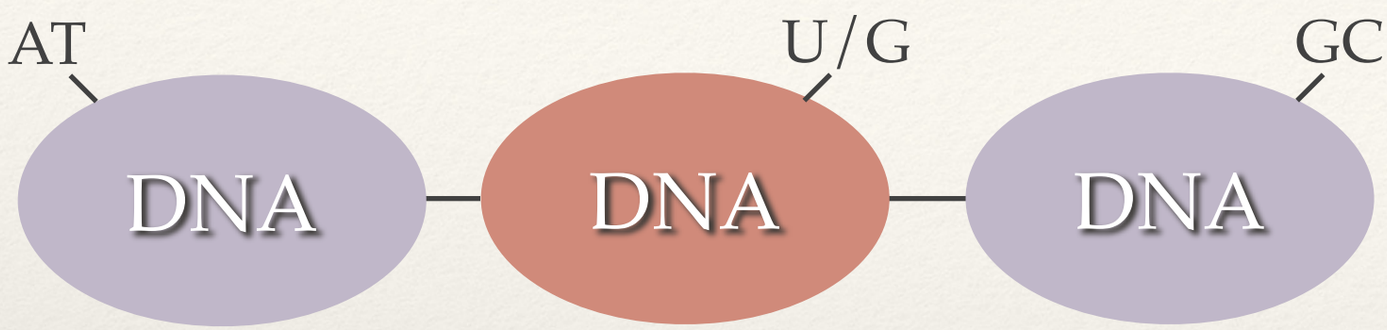
$AP/G(x) := \mathbf{DNA}(x) \wedge$ ● (x)



$U/G : 2$ a U/G mismatch in double strand DNA, U:1, G:1

$AP/G : 1$ an AP/G site in double strand DNA, G:1

« Iota »

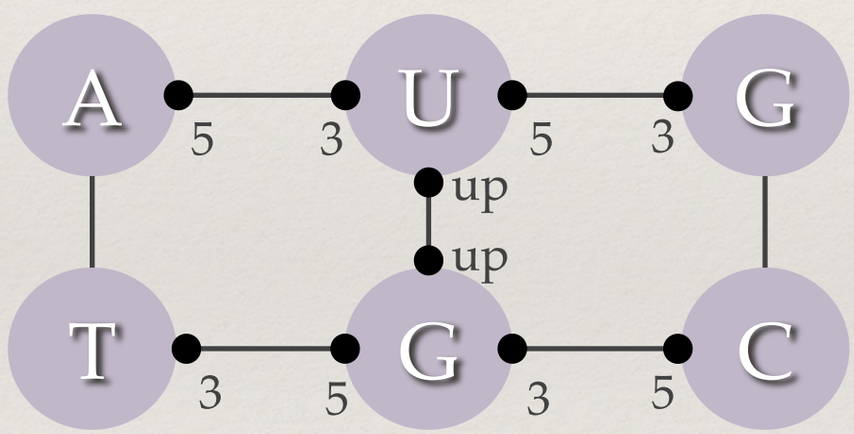


$U/G : 1$ a U/G mismatch in double strand DNA

$AP/G : 1$ an AP/G site in double strand DNA

$$U/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$

$$AP/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$



$U/G : 2$ a U/G mismatch in double strand DNA, U:1, G:1

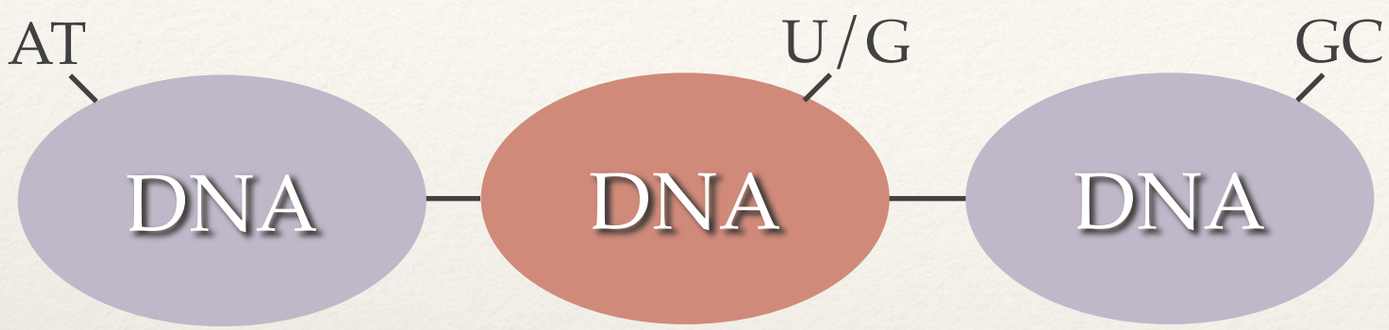
$AP/G : 1$ an AP/G site in double strand DNA, G:1

$$U/G(x, y) := \mathbf{G}(y) \wedge \mathbf{U}(x) \wedge bp(x, y)$$

$$AP/G(x) := \mathbf{G}(x) \wedge \forall u \,.\, \mathbf{Up}(u) \wedge \rho(u) = x \implies free(u)$$

$$\begin{aligned} bp(x, y) &:= Paired(x, y) \\ &\quad \wedge Lig_{\mathbf{3}}(x) \wedge Lig_{\mathbf{5}}(x) \wedge Lig_{\mathbf{3}}(y) \wedge Lig_{\mathbf{5}}(y) \\ Paired(x, y) &:= \exists u, u' \,.\, \rho(u) = x \wedge \rho(u') = y \\ &\quad \wedge \mathbf{Up}(u) \frown \mathbf{Up}(u') \\ Lig_{\mathbf{5}}(x) &:= \exists y, z \,.\, \rho(y) = x \wedge \mathbf{5}(y) \frown \mathbf{3}(z) \\ Lig_{\mathbf{3}}(x) &:= \exists y, z \,.\, \rho(y) = x \wedge \mathbf{3}(y) \frown \mathbf{5}(z) \end{aligned}$$

« Iota »

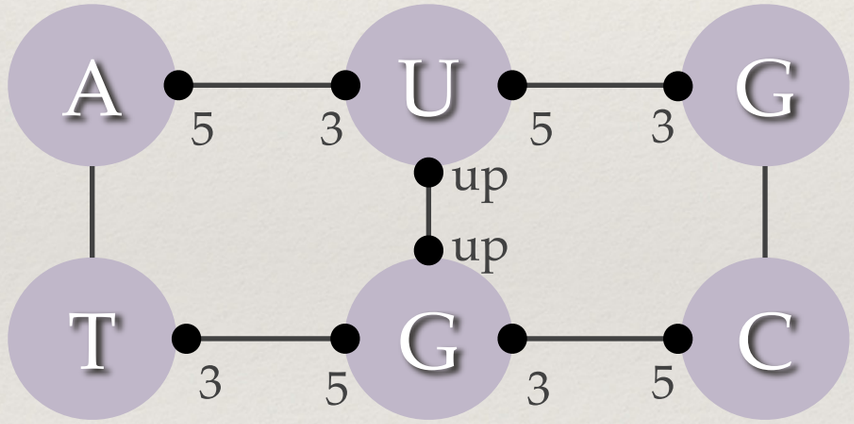


$U/G : 1$ a U/G mismatch in double strand DNA

$AP/G : 1$ an AP/G site in double strand DNA

$$U/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$

$$AP/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$



$U/G : 2$ a U/G mismatch in double strand DNA, U:1, G:1

$AP/G : 1$ an AP/G site in double strand DNA, G:1

$$U/G(x, y) := \mathbf{G}(y) \wedge \mathbf{U}(x) \wedge bp(x, y)$$

$$AP/G(x) := \mathbf{G}(x) \wedge \forall u \,.\, \mathbf{Up}(u) \wedge \rho(u) = x \implies free(u)$$

« UDG turns U/G mismatch into AP/G »

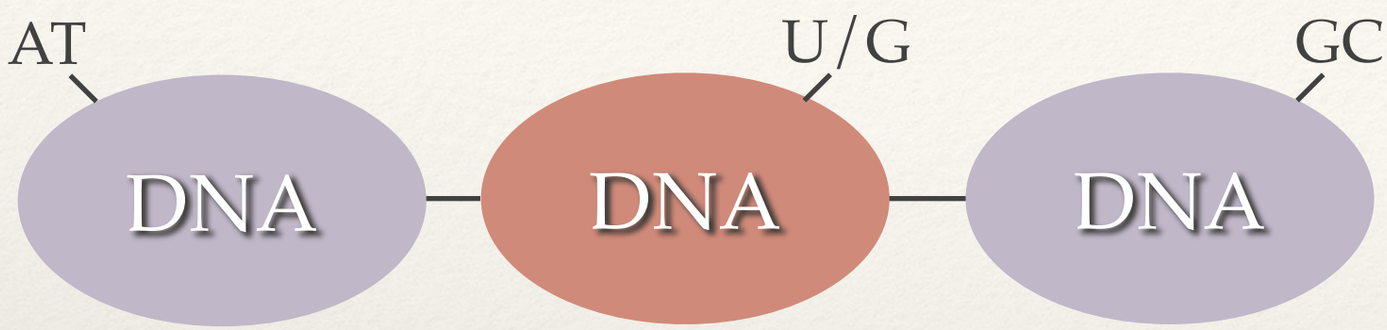
$$bp(x, y) := Paired(x, y) \wedge Lig_3(x) \wedge Lig_5(x) \wedge Lig_3(y) \wedge Lig_5(y)$$

$$Paired(x, y) := \exists u, u' \,.\, \rho(u) = x \wedge \rho(u') = y \wedge \mathbf{Up}(u) \frown \mathbf{Up}(u')$$

$$Lig_5(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{5}(y) \frown \mathbf{3}(z)$$

$$Lig_3(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{3}(y) \frown \mathbf{5}(z)$$

« Iota »

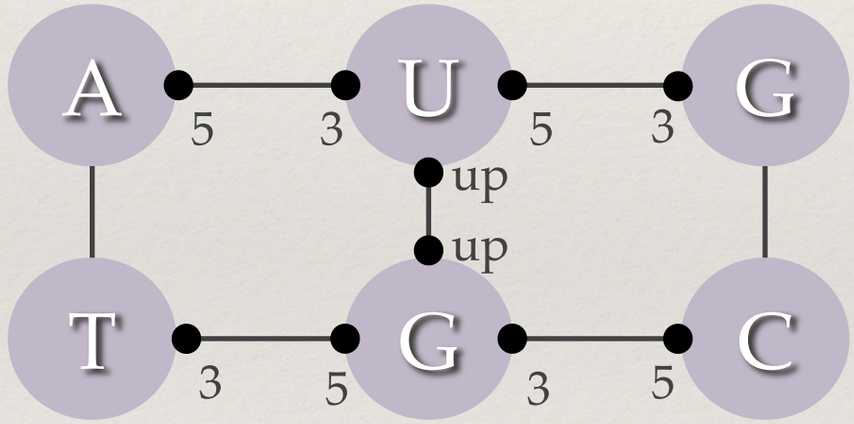


$U/G : 1$ a U/G mismatch in double strand DNA

$AP/G : 1$ an AP/G site in double strand DNA

$$U/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$

$$AP/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$



$U/G : 2$ a U/G mismatch in double strand DNA, U:1, G:1

$AP/G : 1$ an AP/G site in double strand DNA, G:1

$$U/G(x, y) := \mathbf{G}(y) \wedge \mathbf{U}(x) \wedge bp(x, y)$$

$$AP/G(x) := \mathbf{G}(x) \wedge \forall u \,.\, \mathbf{Up}(u) \wedge \rho(u) = x \implies free(u)$$

« UDG turns U/G mismatch into AP/G »

$$\mathtt{U/G(x)} \frown \mathbf{UDG}(\mathtt{y}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

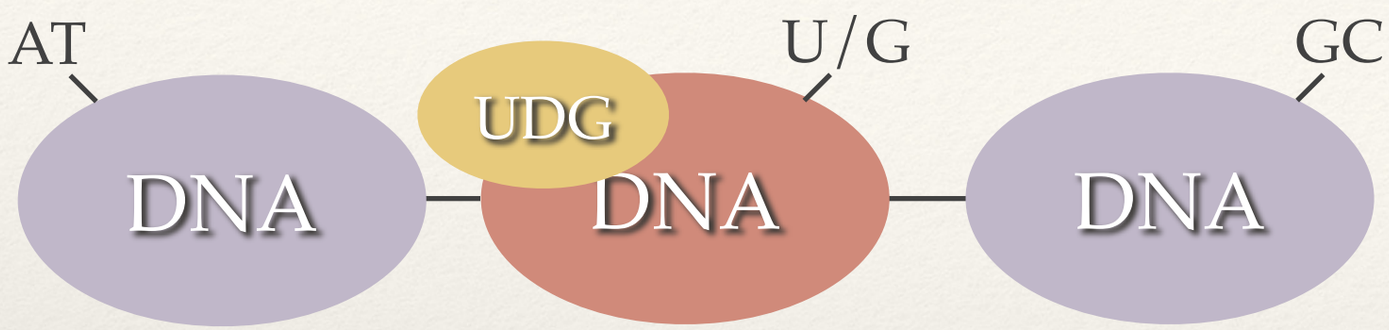
$$bp(x, y) := Paired(x, y) \wedge Lig_3(x) \wedge Lig_5(x) \wedge Lig_3(y) \wedge Lig_5(y)$$

$$Paired(x, y) := \exists u, u' \,.\, \rho(u) = x \wedge \rho(u') = y \wedge \mathbf{Up}(u) \frown \mathbf{Up}(u')$$

$$Lig_5(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{5}(y) \frown \mathbf{3}(z)$$

$$Lig_3(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{3}(y) \frown \mathbf{5}(z)$$

« Iota »

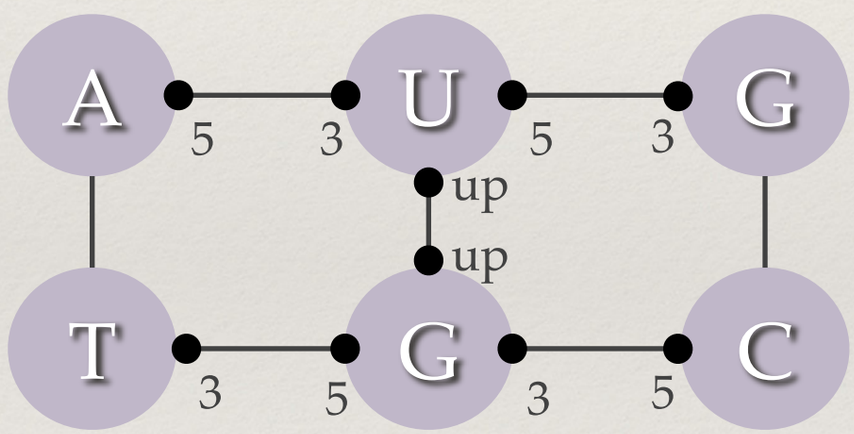


$U/G : 1$ a U/G mismatch in double strand DNA

$AP/G : 1$ an AP/G site in double strand DNA

$$U/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$

$$AP/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$



$U/G : 2$ a U/G mismatch in double strand DNA, U:1, G:1

$AP/G : 1$ an AP/G site in double strand DNA, G:1

$$U/G(x, y) := \mathbf{G}(y) \wedge \mathbf{U}(x) \wedge bp(x, y)$$

$$AP/G(x) := \mathbf{G}(x) \wedge \forall u \,.\, \mathbf{Up}(u) \wedge \rho(u) = x \implies free(u)$$

« UDG turns U/G mismatch into AP/G »

$$\mathtt{U/G(x)} \frown \mathbf{UDG}(\mathtt{y}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

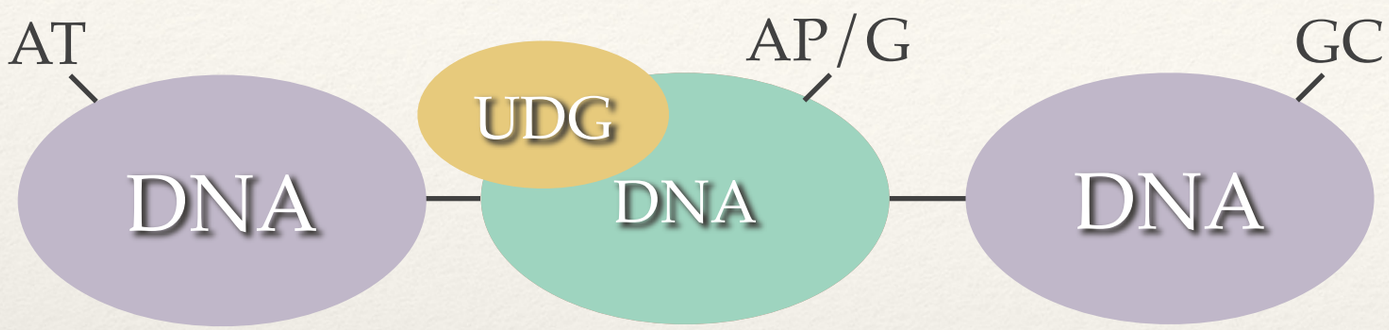
$$bp(x, y) := Paired(x, y) \wedge Lig_3(x) \wedge Lig_5(x) \wedge Lig_3(y) \wedge Lig_5(y)$$

$$Paired(x, y) := \exists u, u' \,.\, \rho(u) = x \wedge \rho(u') = y \wedge \mathbf{Up}(u) \frown \mathbf{Up}(u')$$

$$Lig_5(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{5}(y) \frown \mathbf{3}(z)$$

$$Lig_3(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{3}(y) \frown \mathbf{5}(z)$$

« Iota »

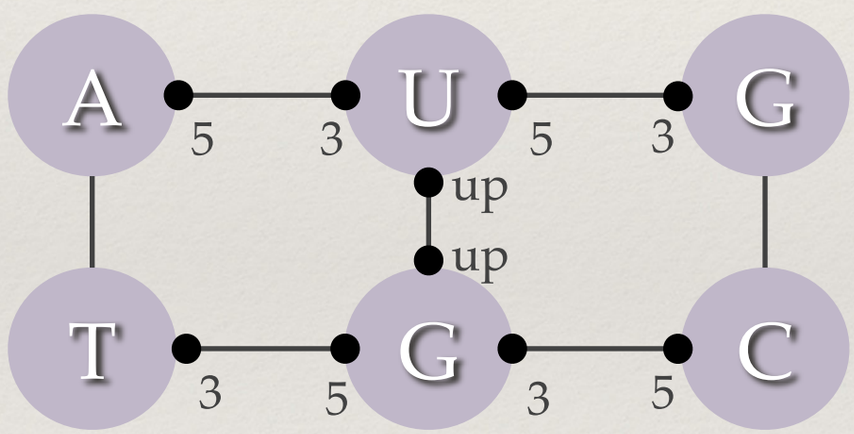


$U/G : 1$ a U/G mismatch in double strand DNA

$AP/G : 1$ an AP/G site in double strand DNA

$$U/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$

$$AP/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$



$U/G : 2$ a U/G mismatch in double strand DNA, U:1, G:1

$AP/G : 1$ an AP/G site in double strand DNA, G:1

$$U/G(x, y) := \mathbf{G}(y) \wedge \mathbf{U}(x) \wedge bp(x, y)$$

$$AP/G(x) := \mathbf{G}(x) \wedge \forall u \,.\, \mathbf{Up}(u) \wedge \rho(u) = x \implies free(u)$$

« UDG turns U/G mismatch into AP/G »

$$\mathtt{U/G(x)} \frown \mathbf{UDG}(\mathtt{y}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

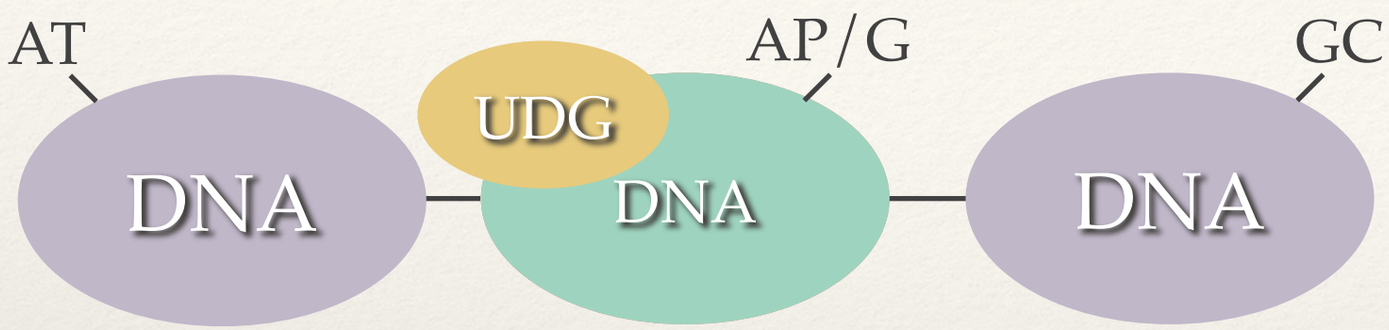
$$bp(x, y) := Paired(x, y) \wedge Lig_3(x) \wedge Lig_5(x) \wedge Lig_3(y) \wedge Lig_5(y)$$

$$Paired(x, y) := \exists u, u' \,.\, \rho(u) = x \wedge \rho(u') = y \wedge \mathbf{Up}(u) \frown \mathbf{Up}(u')$$

$$Lig_5(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{5}(y) \frown \mathbf{3}(z)$$

$$Lig_3(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{3}(y) \frown \mathbf{5}(z)$$

« Iota »

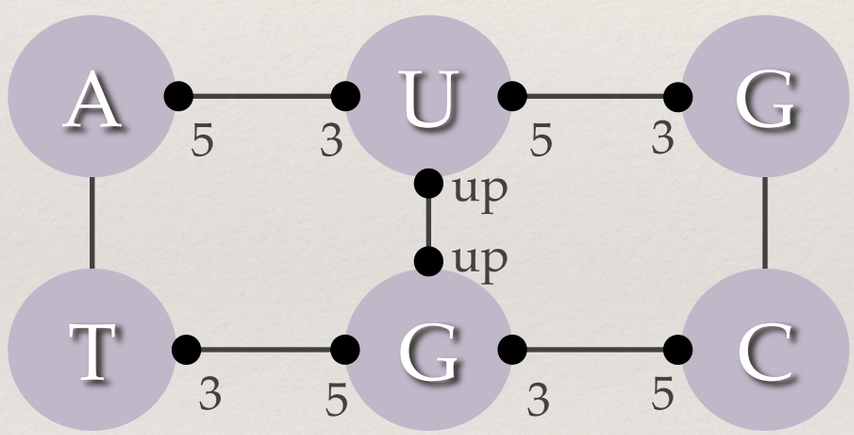


$U/G : 1$ a U/G mismatch in double strand DNA

$AP/G : 1$ an AP/G site in double strand DNA

$$U/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$

$$AP/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$



$U/G : 2$ a U/G mismatch in double strand DNA, U:1, G:1

$AP/G : 1$ an AP/G site in double strand DNA, G:1

$$U/G(x, y) := \mathbf{G}(y) \wedge \mathbf{U}(x) \wedge bp(x, y)$$

$$AP/G(x) := \mathbf{G}(x) \wedge \forall u \,.\, \mathbf{Up}(u) \wedge \rho(u) = x \implies free(u)$$

« UDG turns U/G mismatch into AP/G »

$$\mathtt{U/G(x)} \frown \mathbf{UDG}(\mathtt{y}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

$$\mathtt{U/G(y,x)} \frown \mathbf{UDG}(\mathtt{z}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

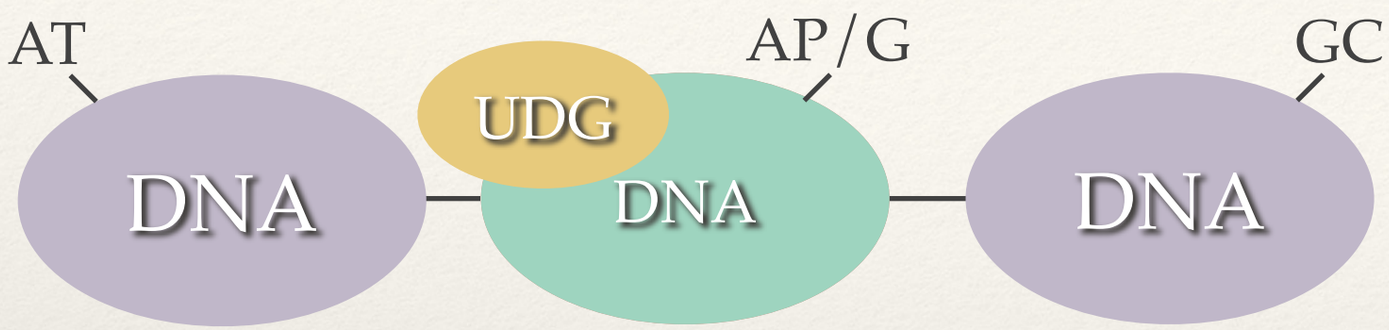
$$bp(x, y) := Paired(x, y) \wedge Lig_3(x) \wedge Lig_5(x) \wedge Lig_3(y) \wedge Lig_5(y)$$

$$Paired(x, y) := \exists u, u' \,.\, \rho(u) = x \wedge \rho(u') = y \wedge \mathbf{Up}(u) \frown \mathbf{Up}(u')$$

$$Lig_5(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{5}(y) \frown \mathbf{3}(z)$$

$$Lig_3(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{3}(y) \frown \mathbf{5}(z)$$

« Iota »

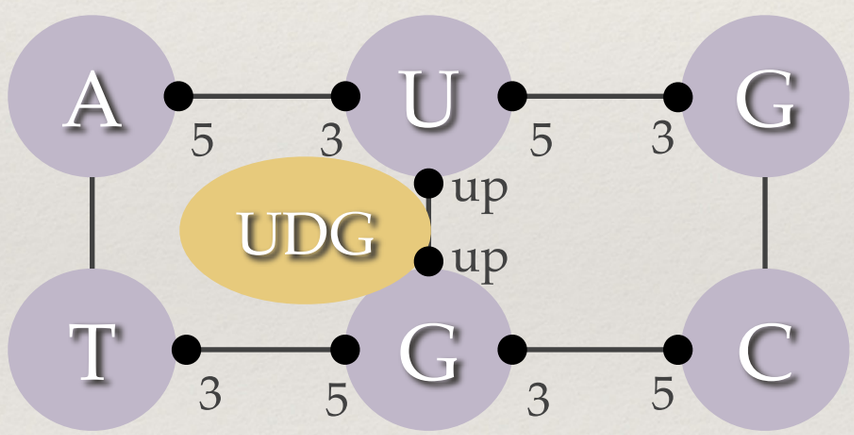


$U/G : 1$ a U/G mismatch in double strand DNA

$AP/G : 1$ an AP/G site in double strand DNA

$$U/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$

$$AP/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$



$U/G : 2$ a U/G mismatch in double strand DNA, U:1, G:1

$AP/G : 1$ an AP/G site in double strand DNA, G:1

$$U/G(x, y) := \mathbf{G}(y) \wedge \mathbf{U}(x) \wedge bp(x, y)$$

$$AP/G(x) := \mathbf{G}(x) \wedge \forall u \,.\, \mathbf{Up}(u) \wedge \rho(u) = x \implies free(u)$$

« UDG turns U/G mismatch into AP/G »

$$\mathtt{U/G(x)} \frown \mathbf{UDG}(\mathtt{y}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

$$\mathtt{U/G(y,x)} \frown \mathbf{UDG}(\mathtt{z}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

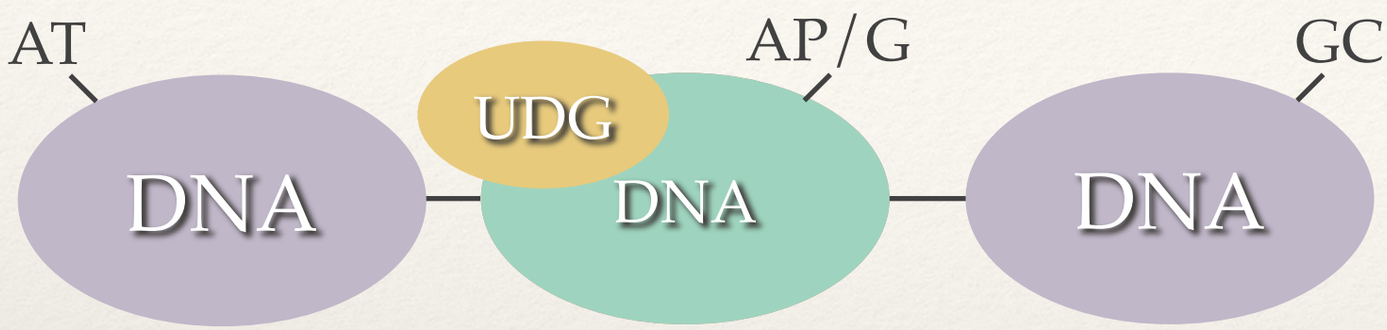
$$bp(x, y) := Paired(x, y) \wedge Lig_3(x) \wedge Lig_5(x) \wedge Lig_3(y) \wedge Lig_5(y)$$

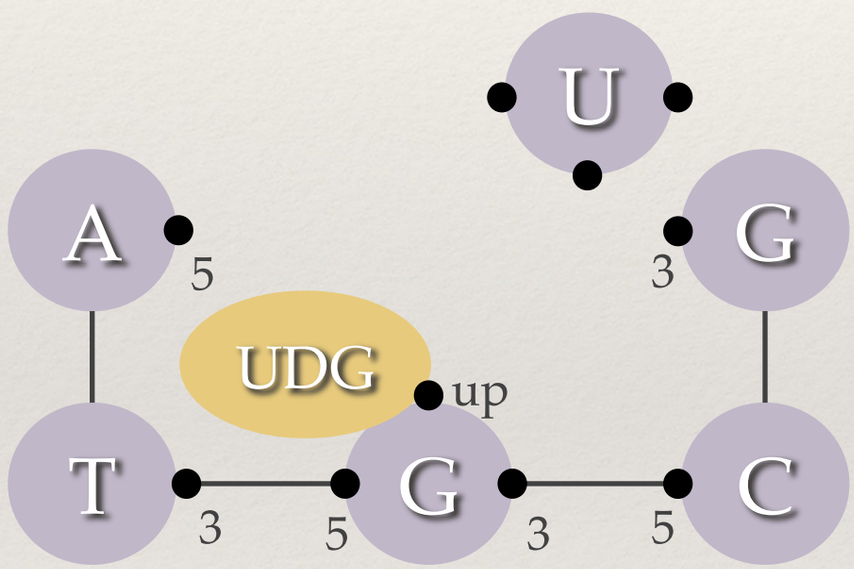
$$Paired(x, y) := \exists u, u' \,.\, \rho(u) = x \wedge \rho(u') = y \wedge \mathbf{Up}(u) \frown \mathbf{Up}(u')$$

$$Lig_5(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{5}(y) \frown \mathbf{3}(z)$$

$$Lig_3(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{3}(y) \frown \mathbf{5}(z)$$

« Iota »





$U/G : 1$ a U/G mismatch in double strand DNA

$AP/G : 1$ an AP/G site in double strand DNA

$$U/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$

$$AP/G(x) := \mathbf{DNA}(x) \wedge \bullet(x)$$

$U/G : 2$ a U/G mismatch in double strand DNA, U:1, G:1

$AP/G : 1$ an AP/G site in double strand DNA, G:1

$$U/G(x, y) := \mathbf{G}(y) \wedge \mathbf{U}(x) \wedge bp(x, y)$$

$$AP/G(x) := \mathbf{G}(x) \wedge \forall u \,.\, \mathbf{Up}(u) \wedge \rho(u) = x \implies free(u)$$

« UDG turns U/G mismatch into AP/G »

$$\mathtt{U/G(x)} \frown \mathbf{UDG}(\mathtt{y}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

$$\mathtt{U/G(y,x)} \frown \mathbf{UDG}(\mathtt{z}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

$$bp(x, y) := Paired(x, y) \wedge Lig_3(x) \wedge Lig_5(x) \wedge Lig_3(y) \wedge Lig_5(y)$$

$$Paired(x, y) := \exists u, u' \,.\, \rho(u) = x \wedge \rho(u') = y \wedge \mathbf{Up}(u) \frown \mathbf{Up}(u')$$

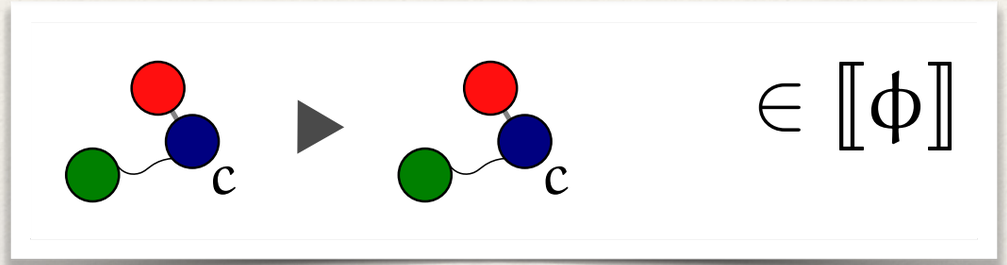
$$Lig_5(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{5}(y) \frown \mathbf{3}(z)$$

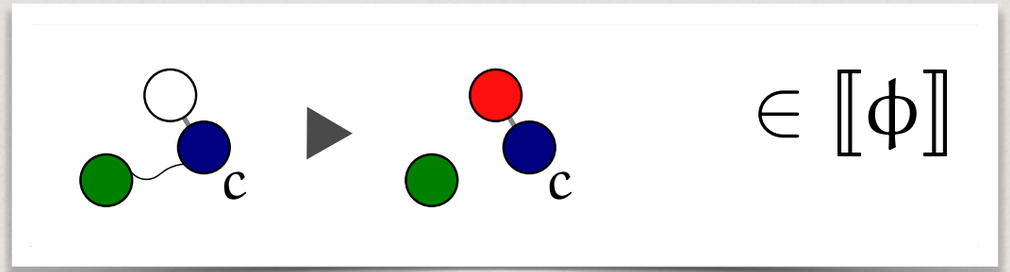
$$Lig_3(x) := \exists y, z \,.\, \rho(y) = x \wedge \mathbf{3}(y) \frown \mathbf{5}(z)$$

« Iota »

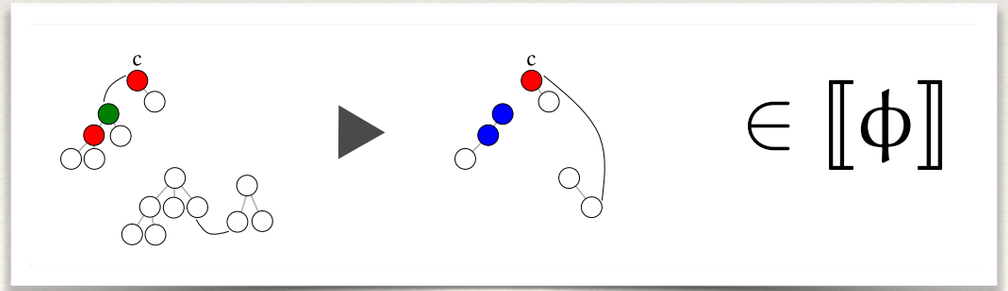
$\exists x.\ c \frown x \wedge \blacksquare^{\star}(c.\mathrm{root}) \qquad \phi$

Full FO with =, pre/post conditions on linked forests

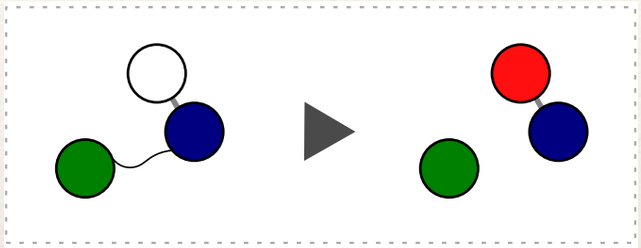


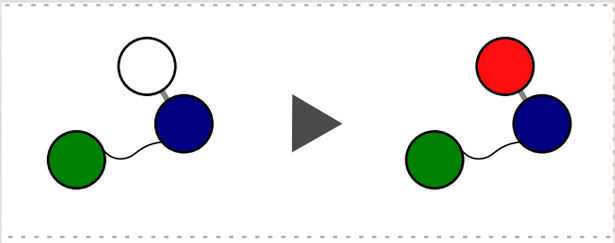


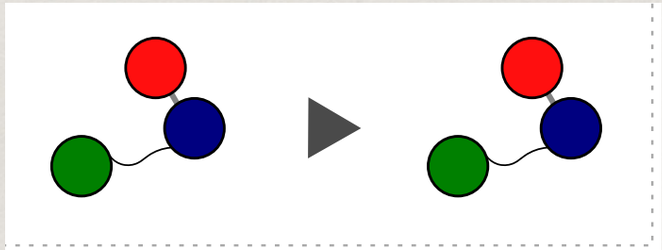
A model is a forest transition

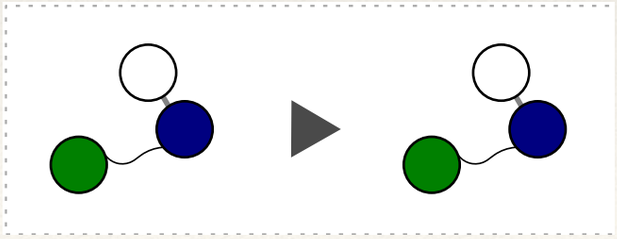


Minimization

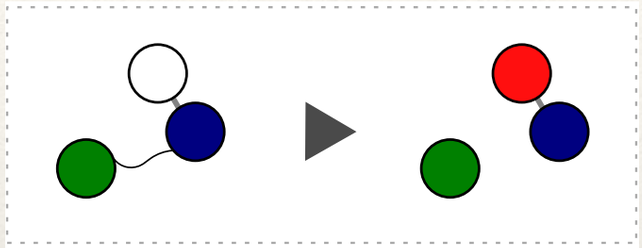


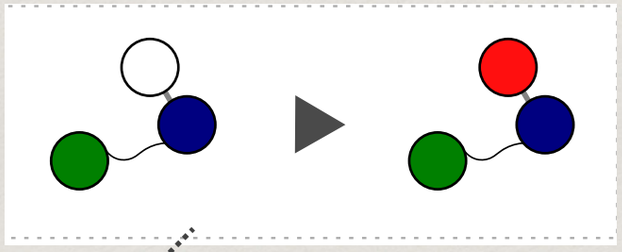


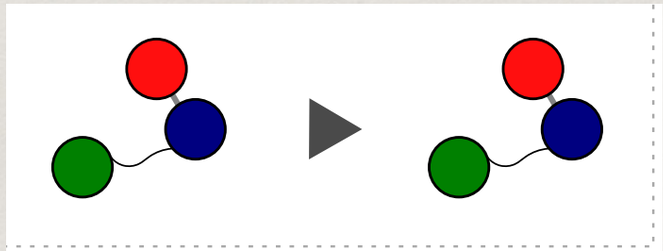


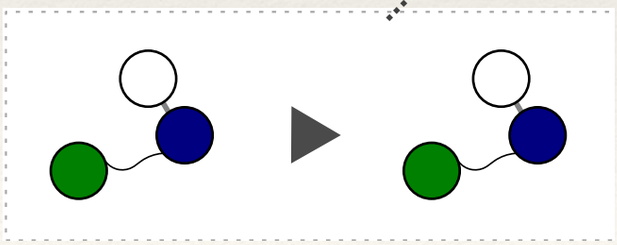


Minimization

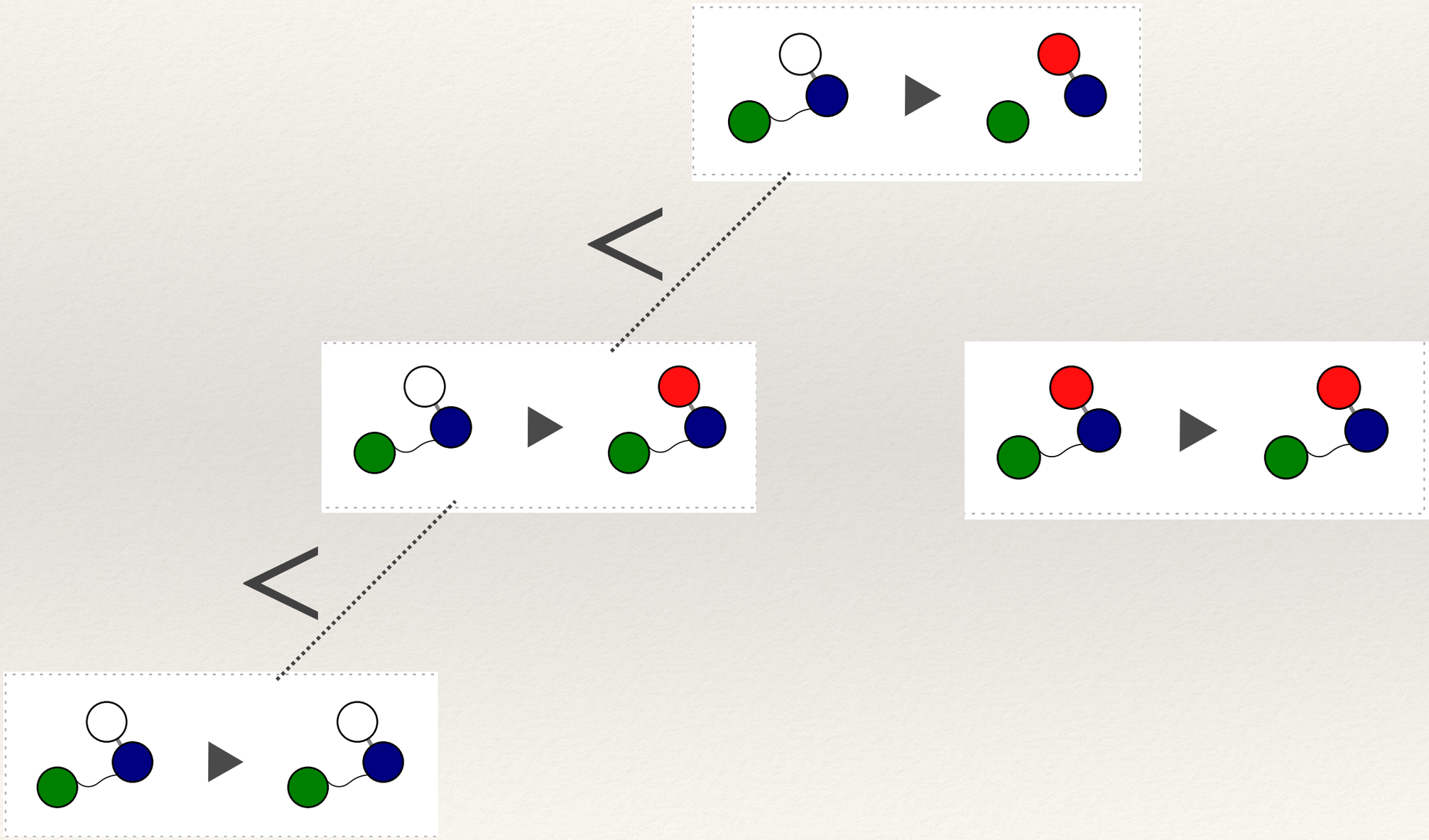




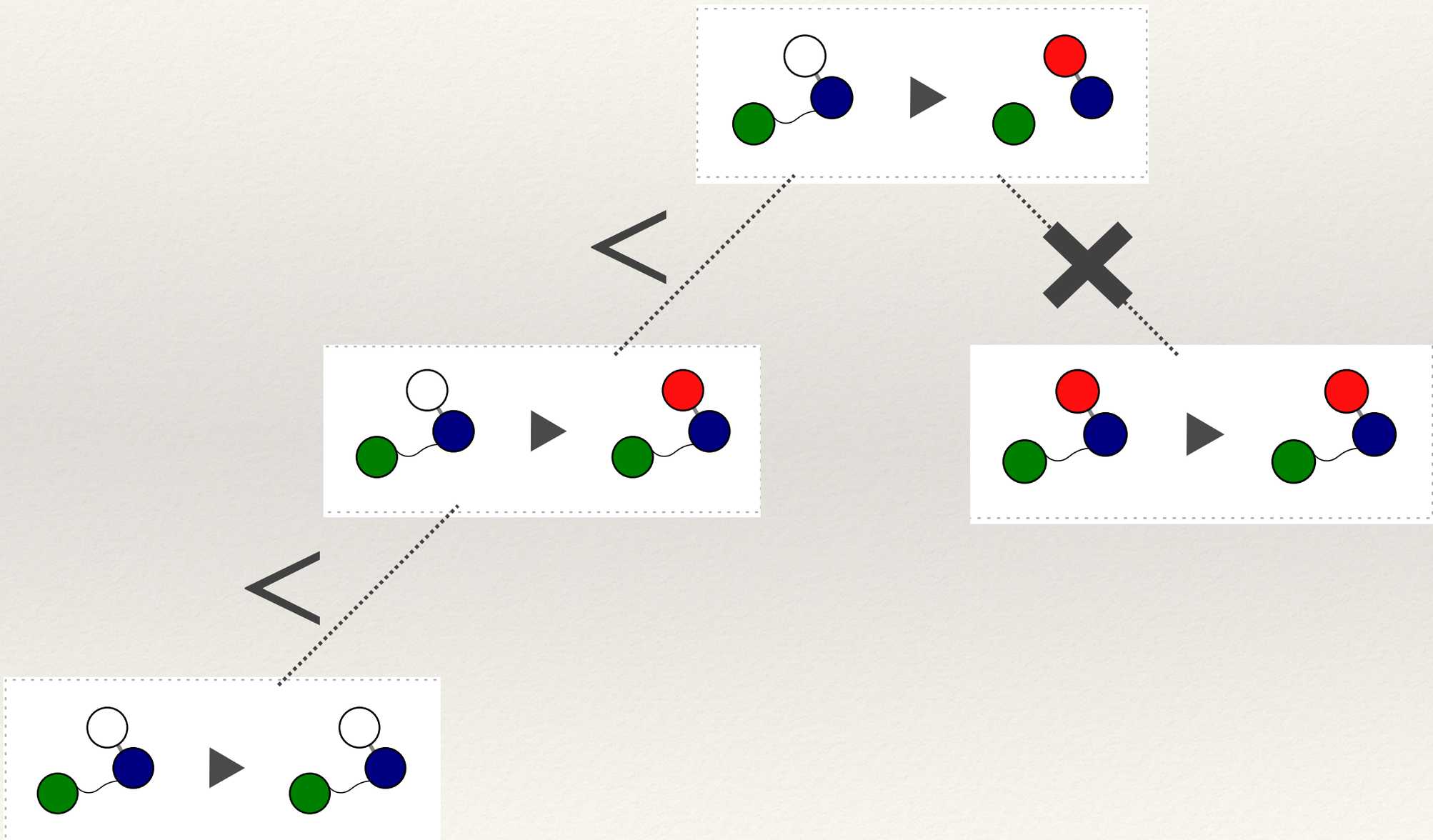




Minimization

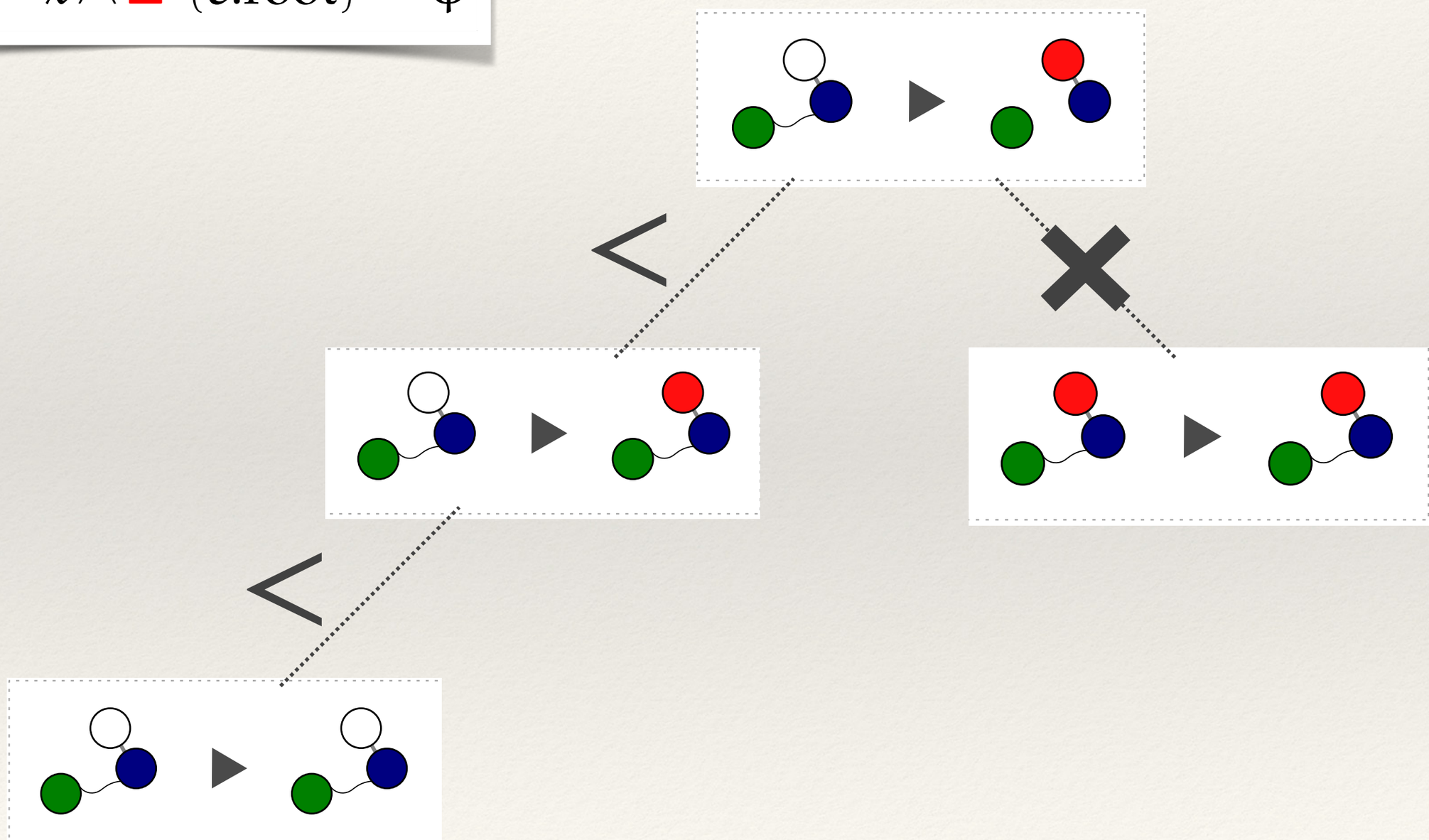


Minimization



Minimization

$\exists x.\ c \frown x \wedge \blacksquare^{\star}(c.\mathrm{root}) \qquad \phi$



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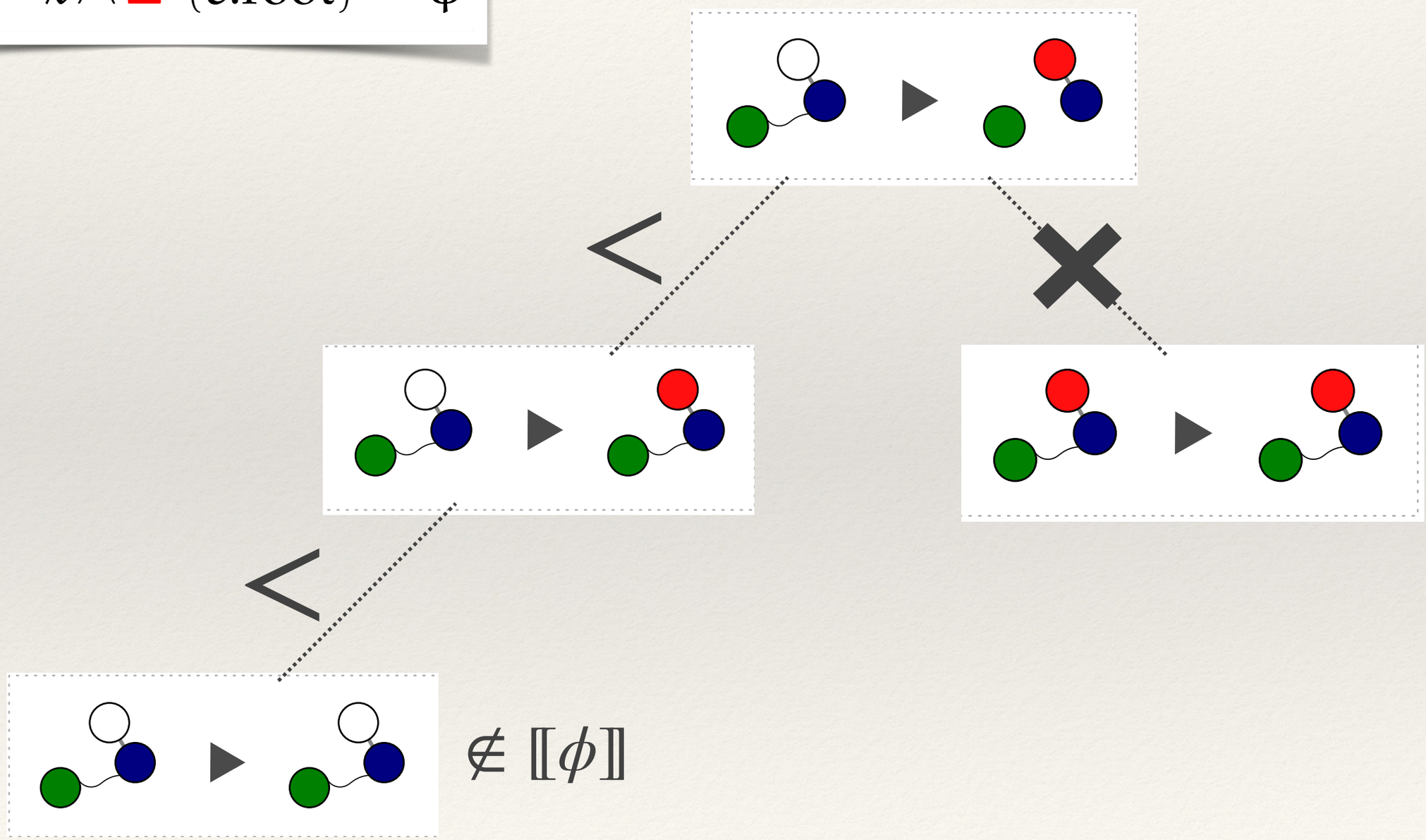
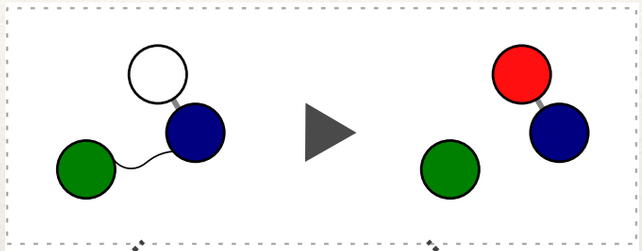
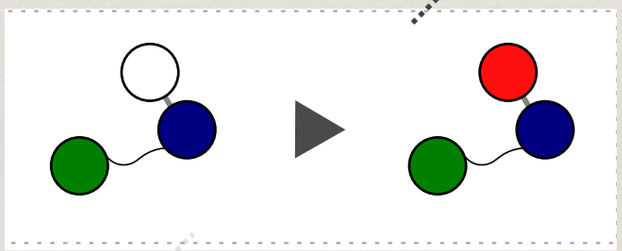
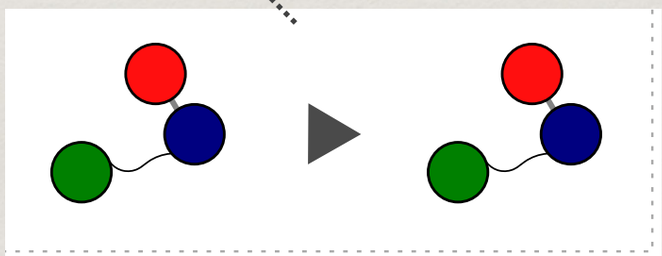


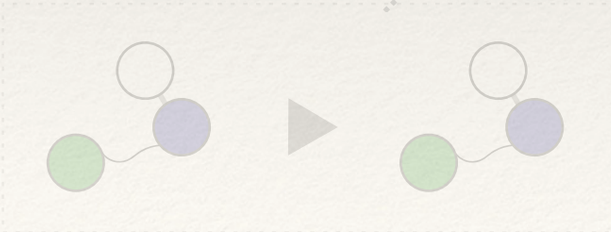
Minimization

$\exists x.\ c \frown x \wedge \blacksquare^{\star}(c.\mathrm{root}) \qquad \phi$





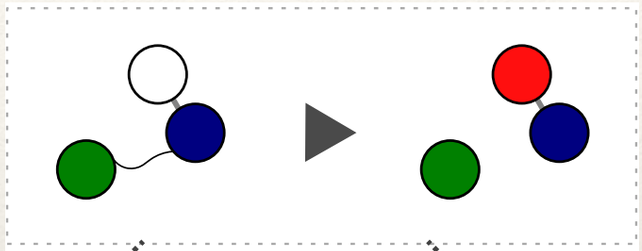




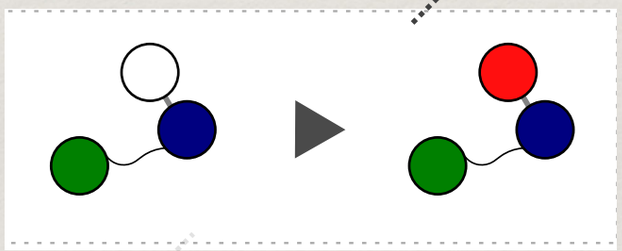
$\notin [\![\phi]\!]$

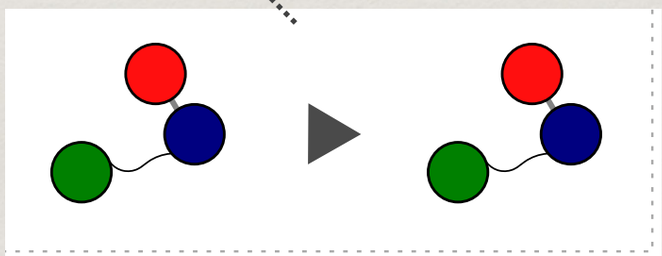
Minimization

$\exists x.\ c \frown x \wedge \blacksquare^{\star}(c.\mathrm{root})$ $\quad \phi$



$\notin [\![\downarrow \phi]\!]$



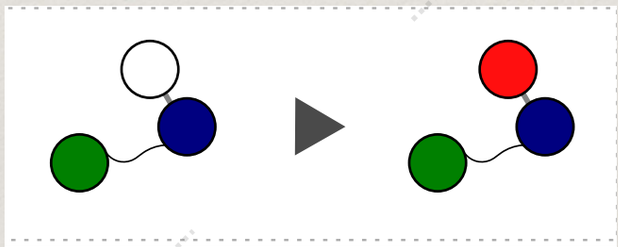


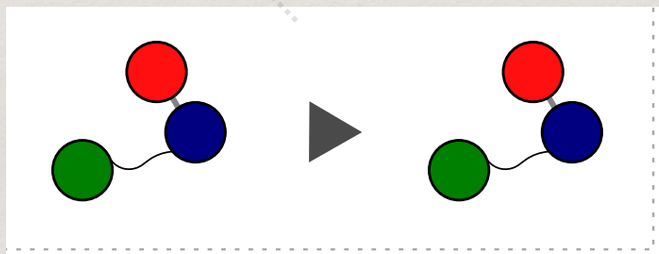
$\notin [\![\phi]\!]$

Minimization

$\exists x.\ c \frown x \wedge \blacksquare^{\star}(c.root) \qquad \phi$

$\notin [\![\downarrow \phi]\!]$





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Minimization

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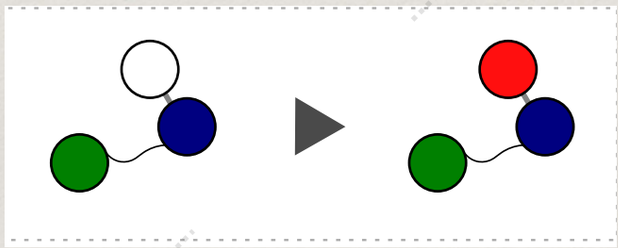
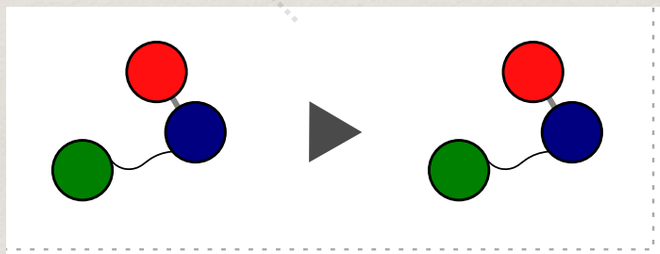
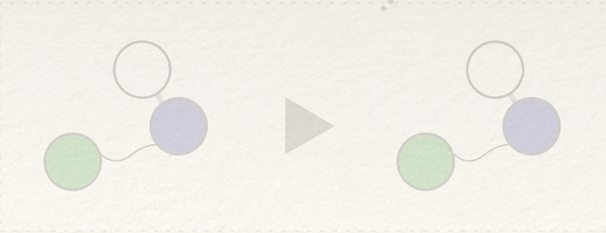
$\notin [\![\downarrow \phi]\!]$





$\in [\![\downarrow \phi]\!]$



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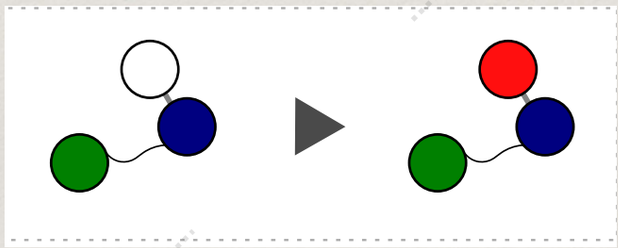
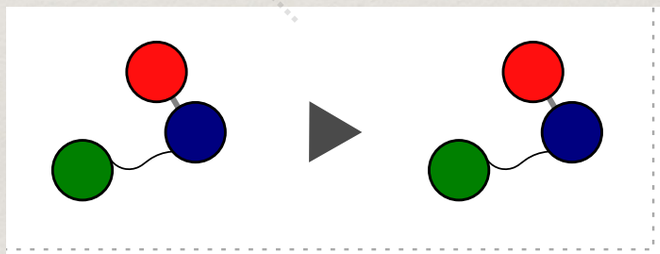


$\in [\![\downarrow \phi]\!]$



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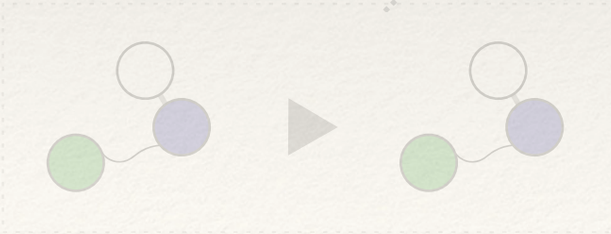


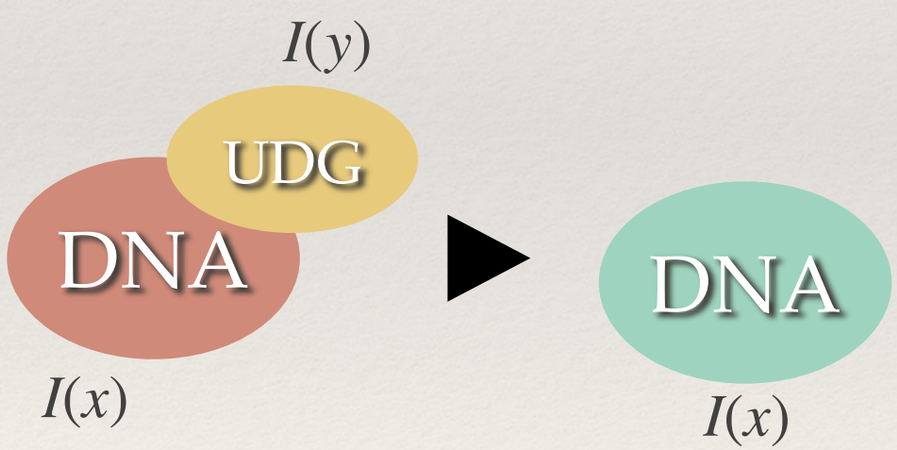
$\notin [\![\phi]\!]$

Synthesis

$$\phi = \mathtt{U/G(x)} \frown \mathbf{UDG}(\mathtt{y}) \wedge \mathtt{AP/G}^{\star}(\mathtt{x})$$

$$U/G(x) := \mathbf{DNA}(x) \wedge \bigcirc(x)$$

$$AP/G(x) := \mathbf{DNA}(x) \wedge \bigcirc(x)$$



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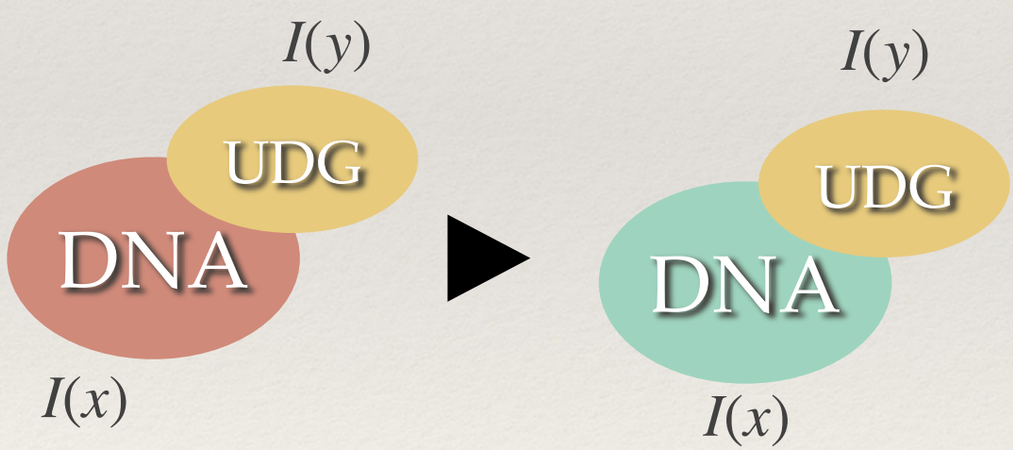

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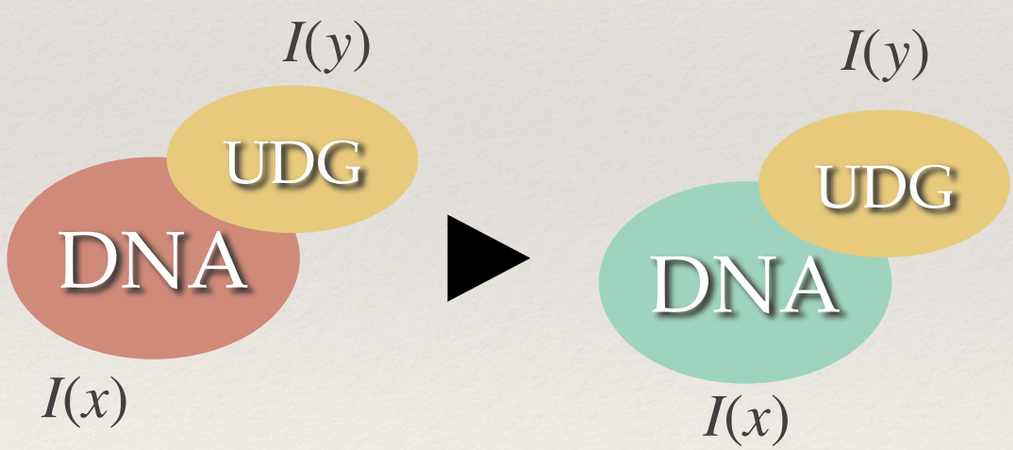

$= [\![\downarrow \phi]\!]$

Synthesis

$\phi = \mathtt{U/G(x)} \frown \mathbf{UDG}(\mathtt{y}) \wedge \mathtt{AP/G^{\star}(x)}$

$\phi = \mathtt{U/G(y,x)} \frown \mathbf{UDG}(\mathtt{z}) \wedge \mathtt{AP/G^{\star}(x)}$

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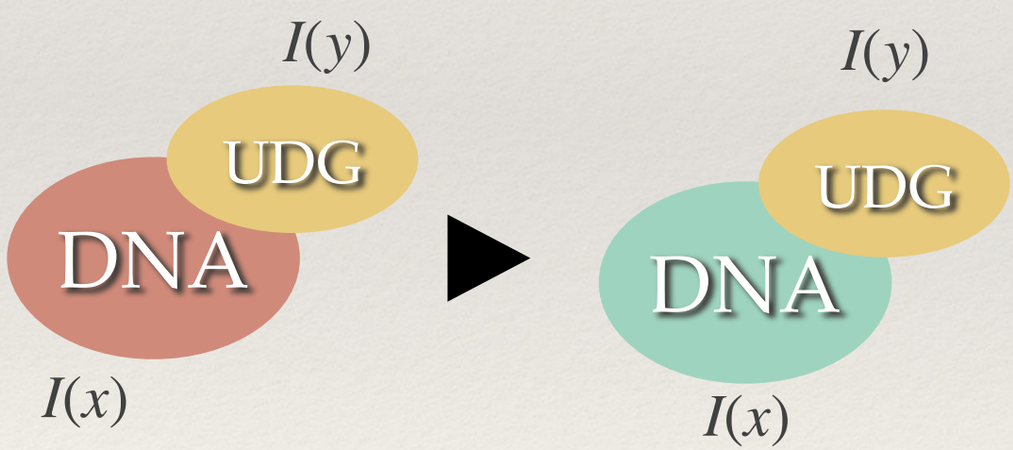

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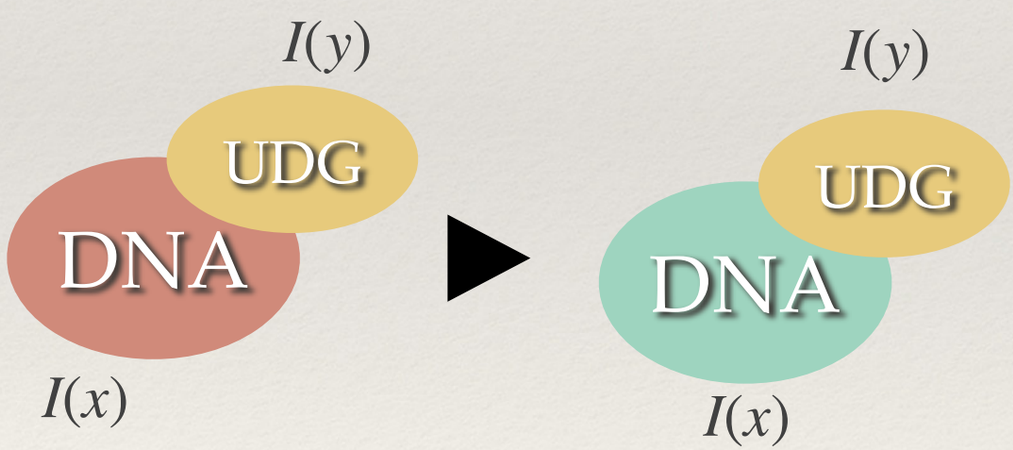
$$AP/G(x) := \mathbf{DNA}(x) \wedge \bigcirc(x)$$

$$U/G(x) := \mathbf{G}(x) \wedge \exists y \,.\, \mathbf{U}(y) \wedge bp(x,y)$$
$$AP/G(x) := \mathbf{G}(x) \wedge \forall u \,.\, \mathbf{Up}(u) \wedge \rho(u) = x \implies free(u)$$



$$= [\![\downarrow \phi]\!]$$

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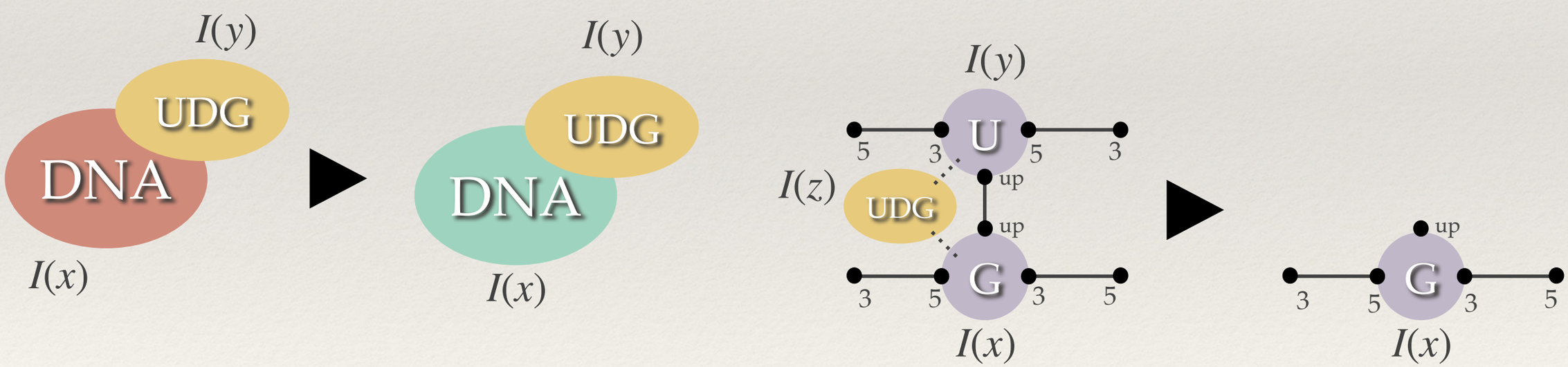

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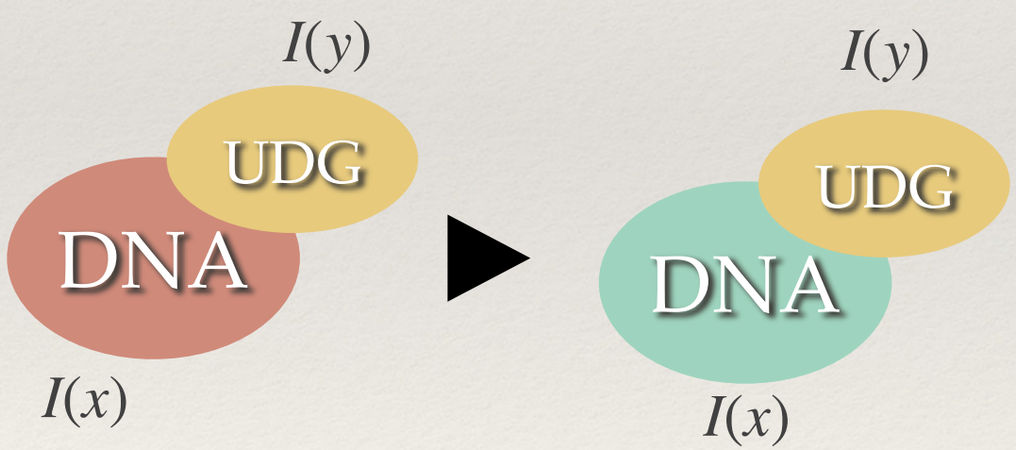

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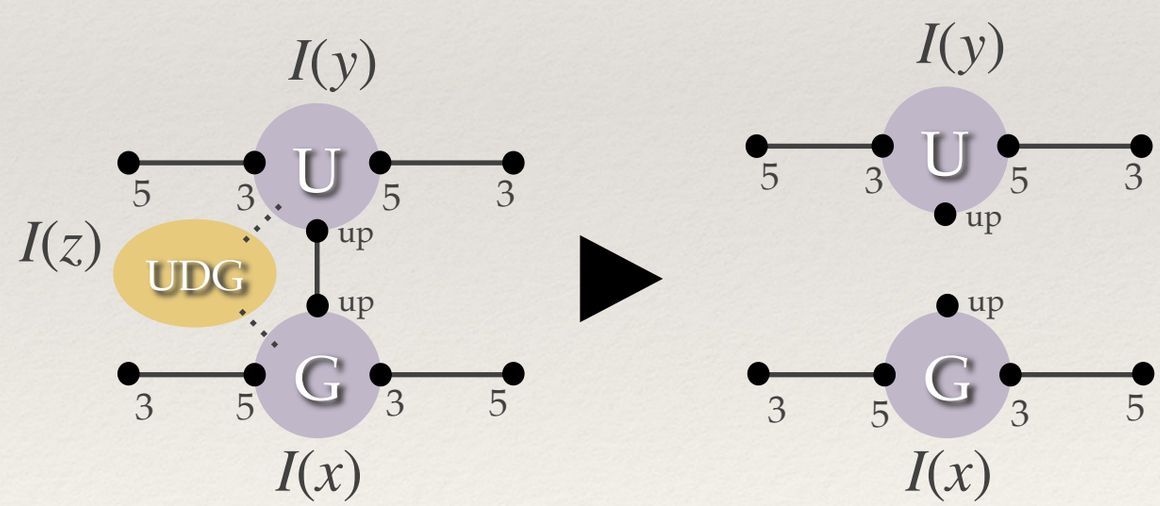

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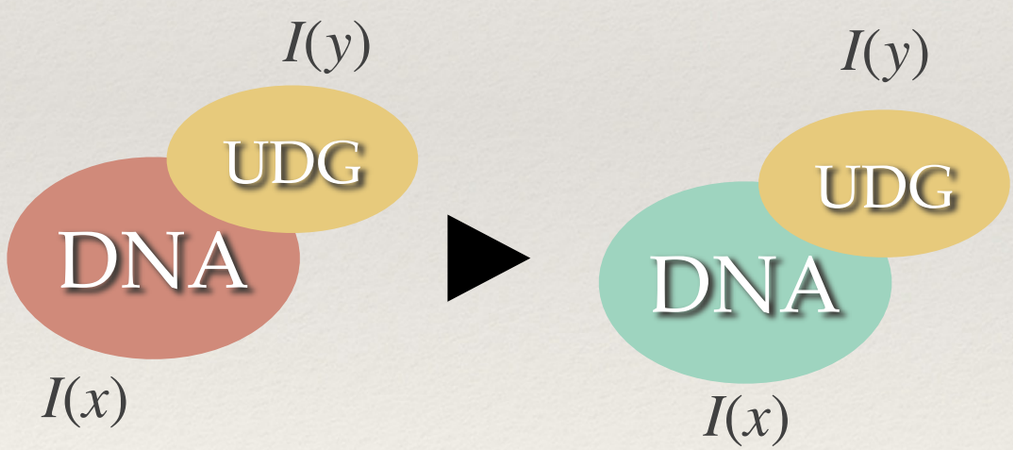

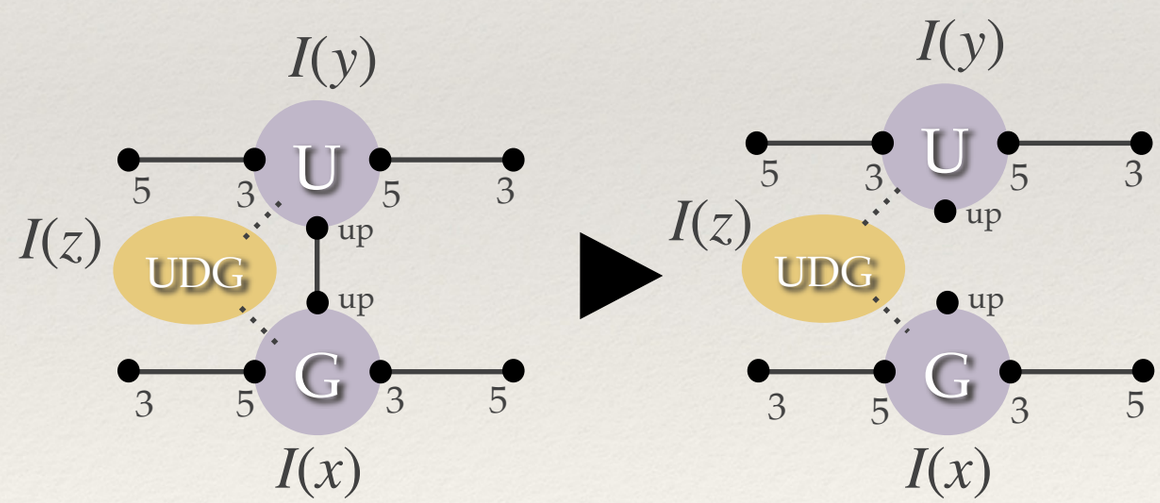

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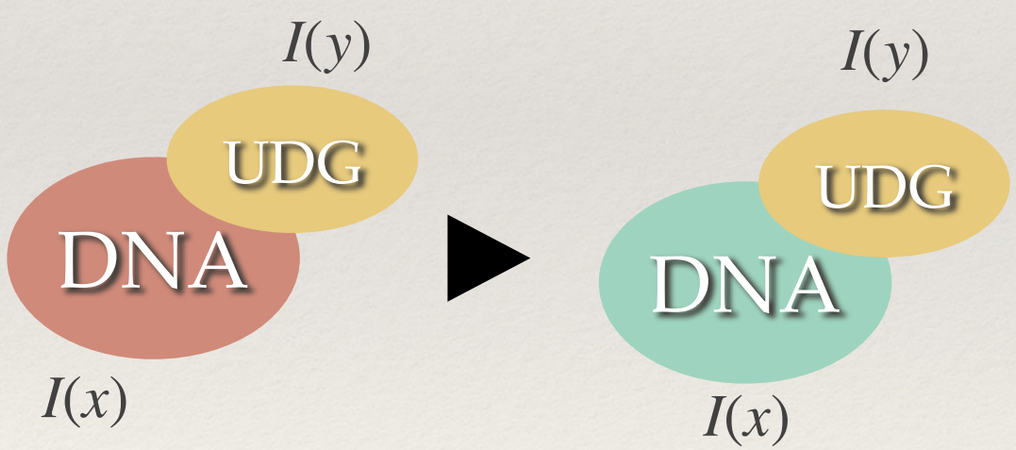

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$$\phi = \mathtt{U/G(y,x)} \frown \mathbf{UDG}(\mathtt{z}) \wedge \mathtt{AP/G^{\star}(x)}$$

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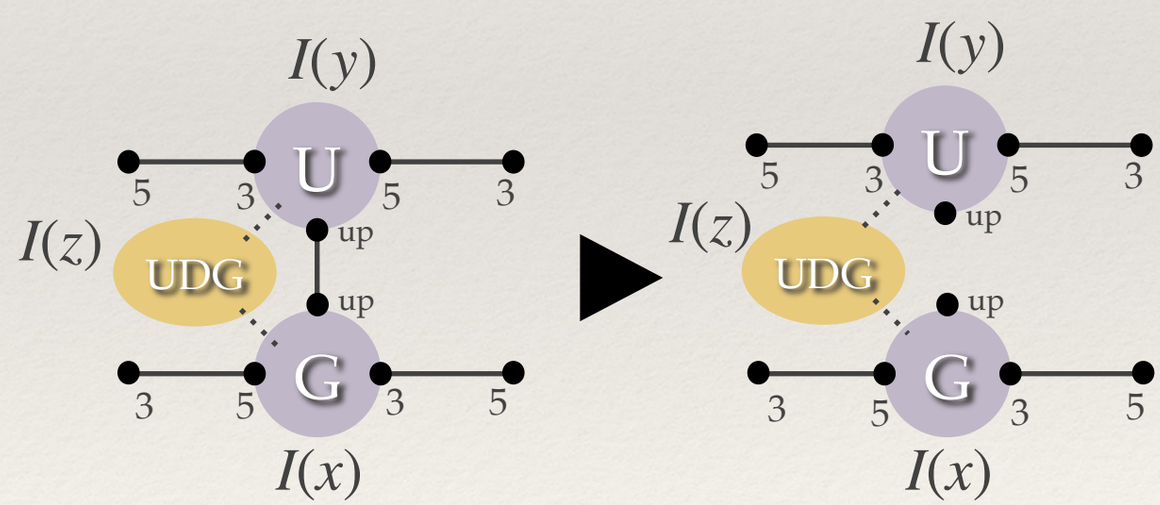

$$= [\![\downarrow \phi]\!]$$

Synthesis

$$\phi = \mathtt{U/G(x)} \frown \mathbf{UDG}(\mathtt{y}) \wedge \mathtt{AP/G^{\star}(x)}$$

$$U/G(x) := \mathbf{DNA}(x) \wedge \bigcirc(x)$$
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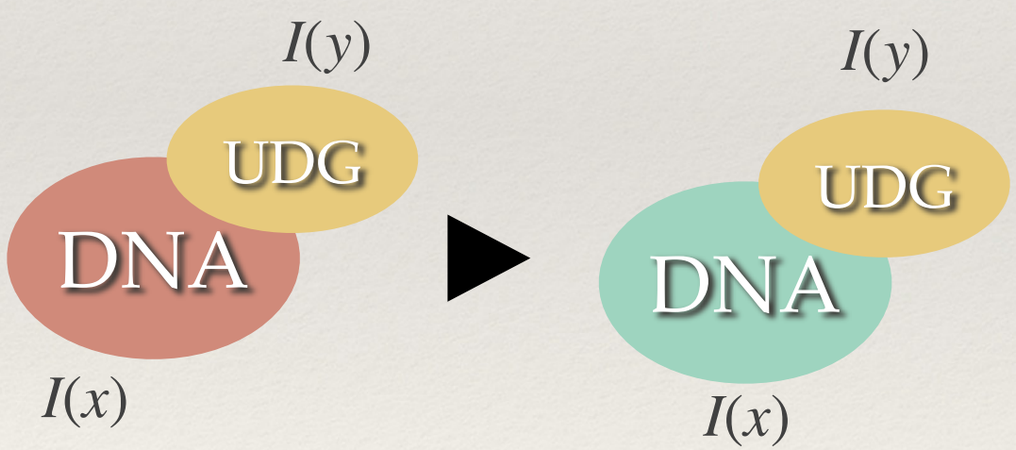

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$$\phi = \mathtt{U/G(y,x)} \frown \mathbf{UDG}(\mathtt{z}) \wedge \mathtt{AP/G^{\star}(x)} \wedge \mathtt{free^{\star}(y)}$$

$$U/G(x) := \mathbf{G}(x) \wedge \exists y \,.\, \mathbf{U}(y) \wedge bp(x,y)$$
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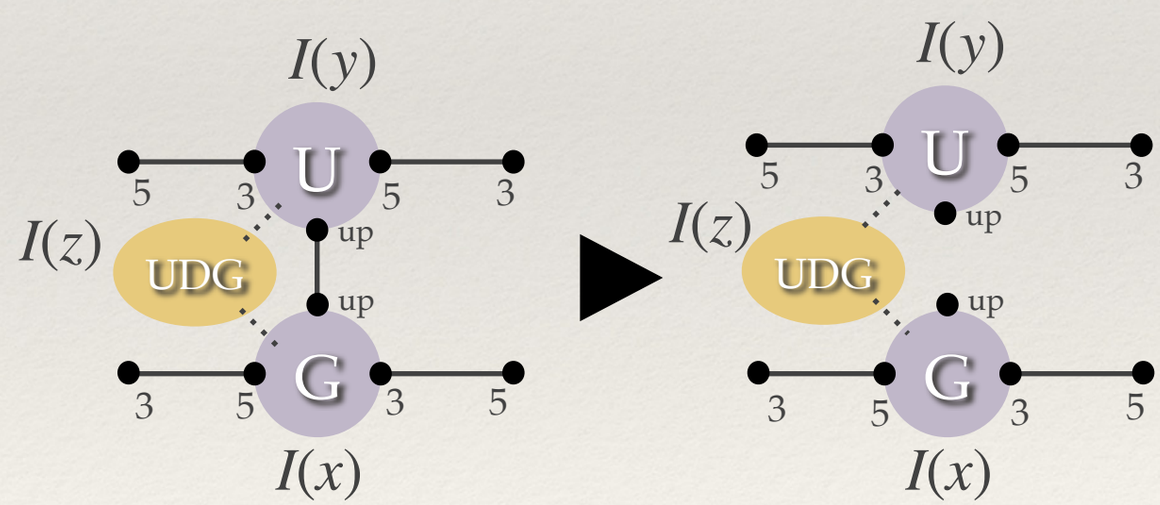

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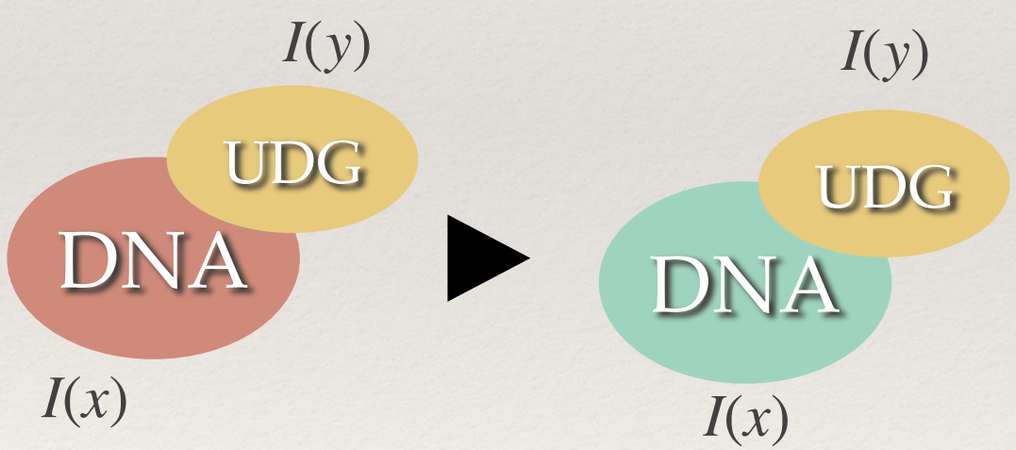

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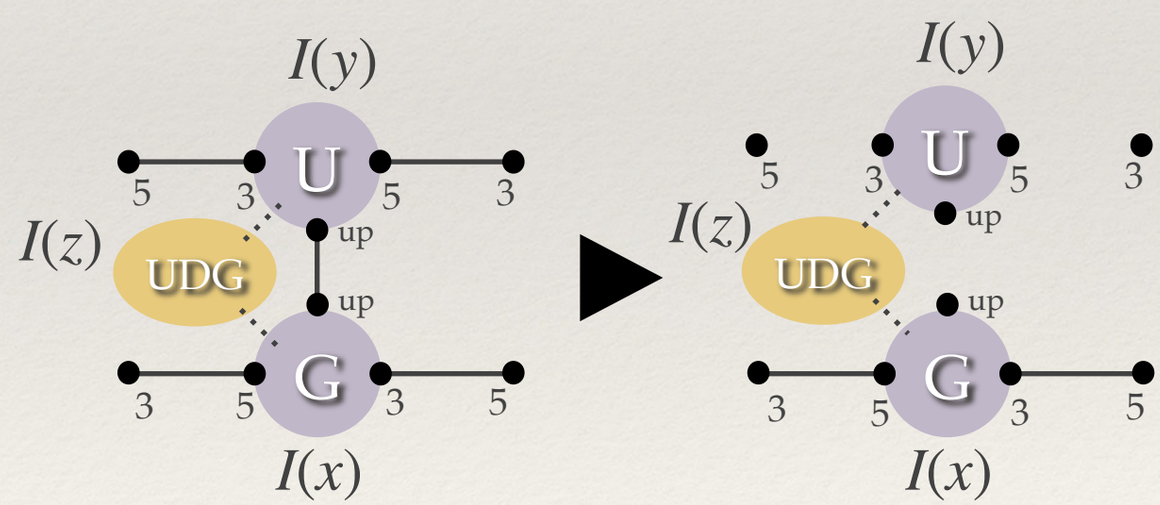

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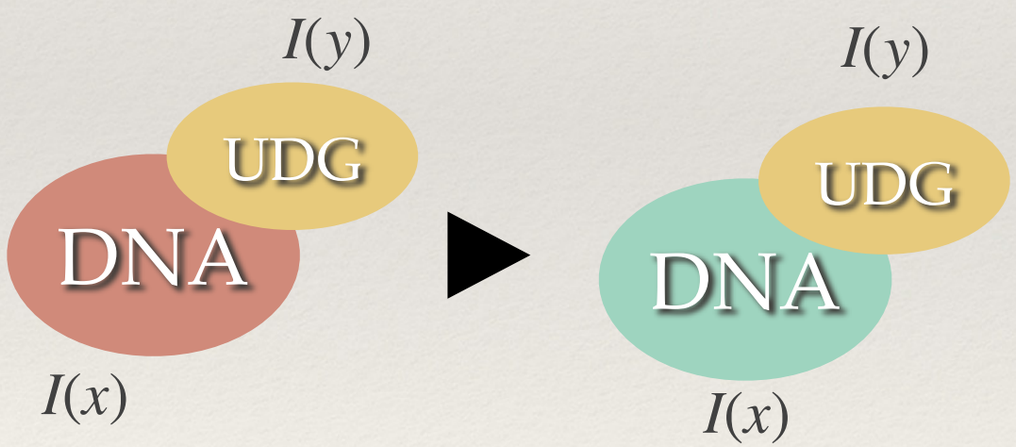
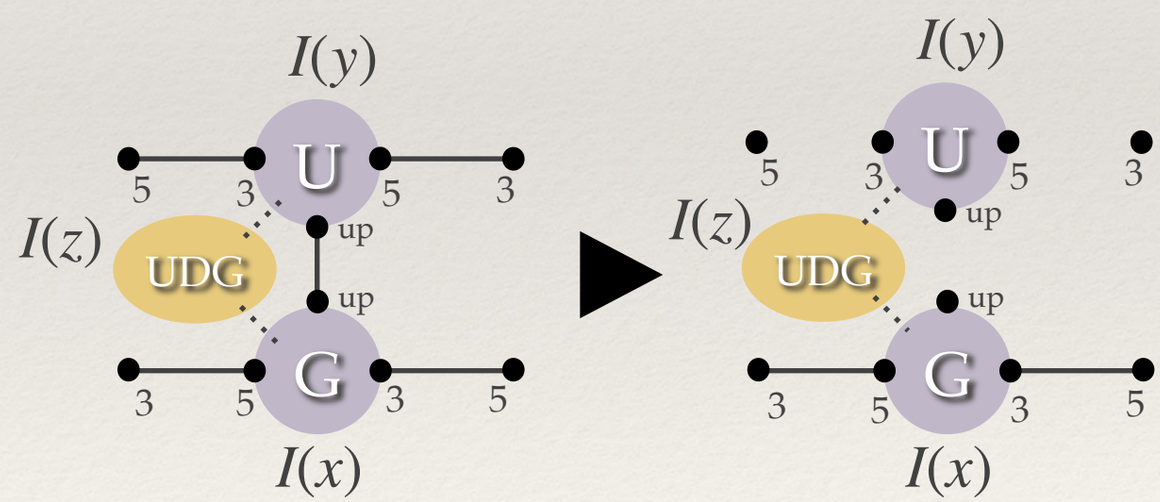
Knowledge needs to be complete
w.r.t abstraction barrier!





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Querying

Structure

Dynamics

Invariants

Knowledge Base

Querying

$\phi_0 := C/G(x) \wedge U/G^\star(x)$

Structure

Dynamics

Invariants

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OK

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OK

let $APE(x) :=$ **APE1**$(x) \vee$ **APE2**(x)

Structure

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APE(x) implies APE1(x) in Str

Structure

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Structure

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Structure

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Structure

Dynamics

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$\phi_0 := C/G(x) \wedge U/G^\star(x)$ — OK

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Structure | Dynamics | Invariants — Knowledge Base

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assert $\forall x, y \,.\, APE(x) \wedge DNA(y) \wedge Bound(x, y) \implies AP(y)$

Structure | Dynamics | Invariants — Knowledge Base

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Structure | Dynamics | Invariants — Knowledge Base

Requirement

A logic to express structure and dynamics of a world represented as bounded linked forests

$A(x) := \exists y \,.\, \rho(y) = x \wedge \mathbf{N}(y)$ $\qquad$ $\phi(x) = A(x) \wedge \exists y \,.\, x \frown^{\star} y$ $\qquad$ $I = \forall x \,.\, A(x) \frown y \implies \mathbf{M}(y)$

Running logical queries

$[\![\phi(x) \wedge \psi(x)]\!] = \varnothing$ $\qquad$ $\phi(x) \wedge I \iff \psi(x) \wedge J$

Internalizing minimization in the logic in order to synthesize graph rewriting rules

$\downarrow \phi(x) \wedge I$ $\qquad$ $\downarrow (\phi(x) \wedge I)$

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Not possible in general!
(minimization requires second order)

Bounding depth of modifications

$$L \in \mathcal{L}_{\mathbf{P}^\star,\mathbf{R}^\star} \quad \frac{}{\langle L \rangle, 0 \vdash L}$$

$$L \in \mathcal{L}_{\mathbf{P},\mathbf{N},\mathbf{R},=} \quad \frac{}{\emptyset, 0 \vdash L}$$

$$\begin{array}{l} \mathcal{V} \subseteq \mathcal{V}' \\ d \leqslant d' \end{array} \quad \frac{\mathcal{V}, d \vdash \phi}{\mathcal{V}', d' \vdash \phi}$$

$$\oplus \in \{\wedge, \vee\} \quad \frac{\mathcal{V}, d \vdash \phi_1 \qquad \mathcal{V}, d \vdash \phi_2}{\mathcal{V}, d \vdash \phi \oplus \phi_1}$$

$$\frac{\mathcal{V}, d \vdash \phi}{\langle \phi \rangle, d \vdash \downarrow(\phi \wedge \mathcal{T}^{n}_{\text{supp}})}$$

$$\langle t \rangle \neq \langle u \rangle \cap (\mathcal{V} \cup \mathcal{V}') \quad \frac{\mathcal{V}, d \vdash \phi \qquad \mathcal{V}', _ \vdash \alpha(t, u)}{(\mathcal{V} \cup \langle u \rangle) \backslash \langle t \rangle, d + |\langle t \rangle \cap \mathcal{V}| \vdash \forall \langle t \rangle.\ \alpha(t, u) \to \phi}$$

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Bounding depth of modifications

A Tractable Logic for Molecular Biology.
A. Husson, J.K, ICLP 2019

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Pipeline

Structure

Dynamics

Invariants

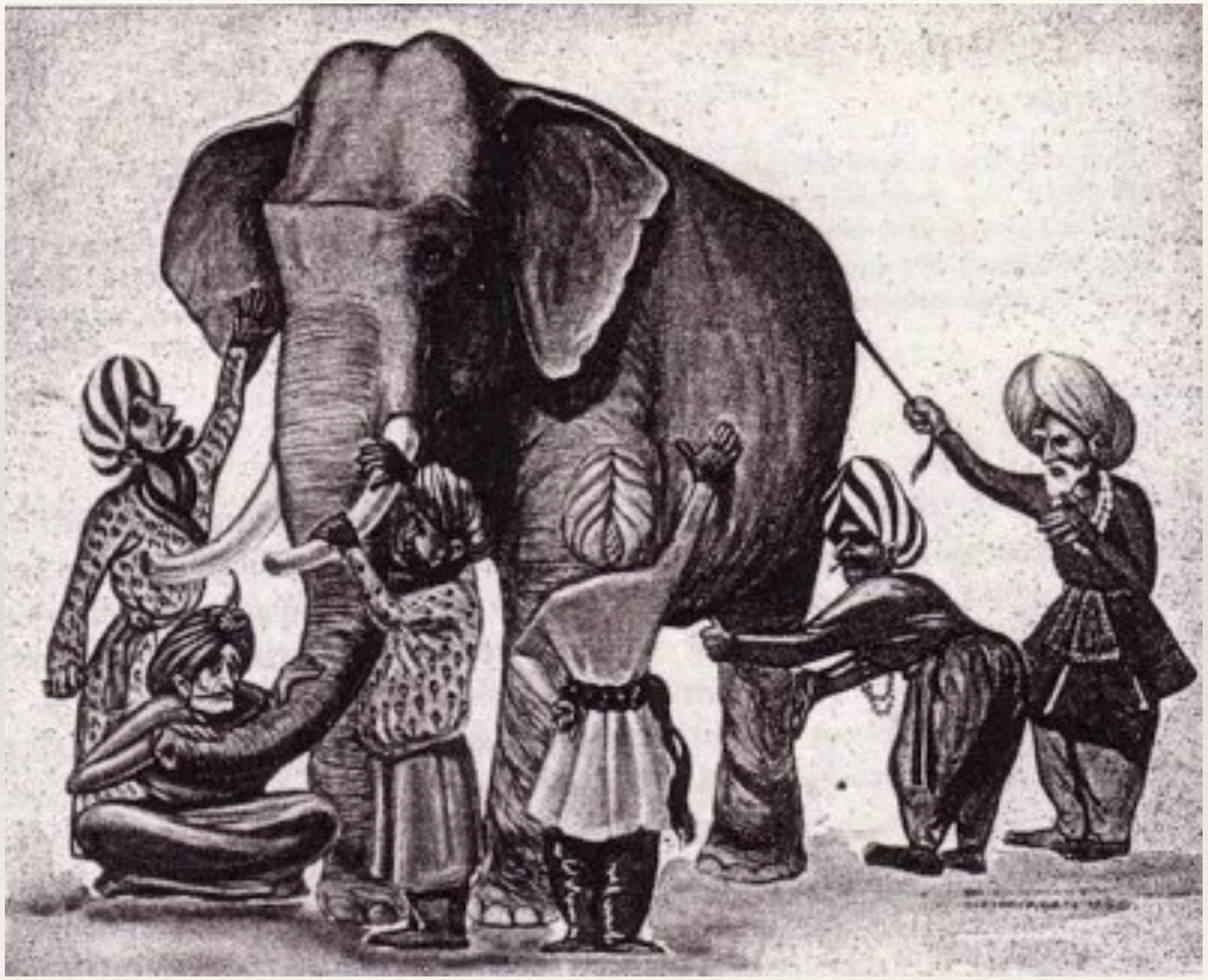
$$\Phi = \bigvee_i \phi_i \qquad \Psi = \bigwedge_i \psi_i$$

$$M = \downarrow (\Phi \wedge \Psi)$$

$[[\,.\,]]$

```
/*'EGFR.EGFR'
  EGFR(L[_],CR[.],N[.],C[.]), EGFR(L[_],CR,[.]N[.],C[.]) ->
  EGFR(L[_],CR[1],N[.],C[.]), EGFR(L[_],CR[1],N[.],C[.]) @ 'k_on'/2*/
'EGFR.EGFR'
  EGF(r[2]), EGFR(L[2],CR[.],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[.],N[.],C[.]) ->
  EGF(r[2]), EGFR(L[2],CR[1],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[1],N[.],C[.]) @
'k_on'/2

/*'EGFR/EGFR' EGFR(L!_,CR!1,N,C), EGFR(L!_,CR!1,N,C) -> EGFR(L!_,CR,N,C),
EGFR(L!_,CR,N,C) @ 'k_off'/2*/
/*'EGFR/EGFR' EGFR(CR!1,N,C), EGFR(CR!1,N,C) -> EGFR(CR,N,C), EGFR(CR,N,C) @
'k_off'/2*/
'EGFR/EGFR'
  EGF(r[2]), EGFR(L[2],CR[1],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[1],N[.],C[.]) ->
  EGF(r[2]), EGFR(L[2],CR[.],N[.],C[.]), EGF(r[3]), EGFR(L[3],CR[.],N[.],C[.]) @
'k_off'/2

'EGF.EGFR' EGF(r[.]), EGFR(L[.],CR[.]) -> EGF(r[1]), EGFR(L[1],CR[.]) @ 'k_on'
'EGF/EGFR' EGF(r[1]), EGFR(L[1],CR[.]) -> EGF(r[.]), EGFR(L[.],CR[.]) @ 'k_off'
'Shc.Grb2' Shc(Y[.]{p}), Grb2(SH2[.]) -> Shc(Y[1]{p}), Grb2(SH2[1]) @ 5*'k_on'
'Shc/Grb2' Shc(Y{p}[1]), Grb2(SH2[1]) -> Shc(Y{p}[.]), Grb2(SH2[.]) @ 'k_off'
'EGFR.Grb2' EGFR(Y1092{p}[.]), Grb2(SH2[.]) -> EGFR(Y1092{p}[1]), Grb2(SH2[1]) @
'k_on'
'EGFR/Grb2' EGFR(Y1092{p}[1]), Grb2(SH2[1]) -> EGFR(Y1092{p}[.]), Grb2(SH2[.]) @
'k_off'
'EGFR.Shc' EGFR(Y1172{p}[.]), Shc(PTB[.]) -> EGFR(Y1172{p}[1]), Shc(PTB[1]) @
'k_on'
'EGFR/Shc' EGFR(Y1172{p}[1]), Shc(PTB[1]) -> EGFR(Y1172{p}[.]), Shc(PTB[.]) @
'k_off'
'Grb2.SoS' Grb2(SH3n[.]), SoS(PR[.],S[.]{u}) -> Grb2(SH3n[1]), SoS(PR[1],S[.]{u})
@ 'k_on'
'Grb2/SoS' Grb2(SH3n[1]), SoS(PR[1]) -> Grb2(SH3n[.]), SoS(PR[.]) @ 'k_off'
'EGFR.int' EGFR(CR[1],N[.],C[.]), EGFR(CR[1],N[.],C[.]) -> EGFR(CR[1],N[2],C[.]),
EGFR(CR[1],N[.],C[2]) @ 'k_on'
'EGFR/int' EGFR(CR[1],N[2],C[.]), EGFR(CR[1],N[.],C[2]) -> EGFR(CR[1],N[.],C[.]),
EGFR(CR[1],N[.],C[.]) @ 'k_off'
'pY1092@EGFR' EGFR(N[1]), EGFR(C[1],Y1092{u}[.]) -> EGFR(N[1]), EGFR(C[1],Y1092{p}
[.]) @ 'k_cat'
'pY1172@EGFR' EGFR(N[1]), EGFR(C[1],Y1172[.]{u}) -> EGFR(N[1]), EGFR(C[1],Y1172[.]
{p}) @ 'k_cat'
'uY1092@EGFR' EGFR(Y1092[.]{p}) -> EGFR(Y1092[.]{u}) @ 'k_cat'
'uY1172@EGFR' EGFR(Y1172{p}[.]) -> EGFR(Y1172{u}[.]) @ 'k_cat'
```

Conclusion